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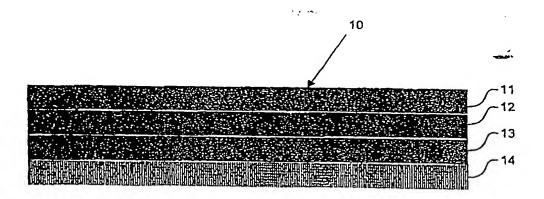
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(54) Title: TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS



(57) Abstract

A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

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TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS

TECHNICAL FIELD

This invention is in the field of transdermal drug delivery devices. More particularly, it relates to a method for making transdermal patches that deliver volatile liquid drugs, such as nicotine, mecamylamine and selegiline, and to the resulting patches. The invention also relates to a method for treating a person for nicotine dependence comprising transdermally administering an effective amount of mecamylamine to the person without transdermal coadministration of nicotine. The invention further relates to a method for treating women for nicotine dependence comprising transdermally co-administering effective doses of mecamylamine and nicotine.

BACKGROUND ART

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There are two basic types of transdermal patches that are used to deliver liquid drugs. One is a liquid reservoir patch in which the liquid drug, either neat or dissolved in a carrier, is confined in a pouch or sac within the device. An example of such a device for delivering nicotine is shown in Fig. 1 of U.S. Pat. No. 5,364,630. The other is a matrix patch in which the liquid drug is dissolved in one or more polymeric layers of a laminated composite. Examples of matrix patches that deliver nicotine are described in U.S. Pat. No. 5,603,947. The present invention relates to a matrix patch.

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In the manufacture of matrix patches for administering volatile liquid drugs such as nicotine it is common to attempt to avoid steps involving heat treatment, e.g., drying, so as to avoid excessive loss or degradation of the drug. For instance U.S. Pat. No. 4,915,950 and 5,603,947 describe a printing procedure whereby neat nicotine is applied to a nonwoven fabric laminated to a polyisobutylene adhesive layer. Alternatively "hot" melt adhesives that melt at relatively low temperatures have been used as a matrix material for these drugs. See U.S. Pat. No. 5,411,739.

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PCT Pub. No. WO 96/40085 describes transdermal matrix patches for administering drugs such as selegiline. nitroglycerin and nicotine, that are liquid at normal room temperature. The publication suggests making a monolithic matrix of the drug in an adhesive by mixing one

or more polymeric adhesives, preferably polyacrylate and polysiloxane, and the drug in a volatile solvent, casting the mixture, and evaporating the solvent. The publication lists as examples of volatile solvents isopropanol, ethanol, xylene, toluene, hexane, cyclohexane, heptane, ethyl acetate and butyl acetate.

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When silicone adhesives have been used as the matrix material in nicotine patches the matrix layer has been cast from a heptane solution. See, for instance, Example 1 of U.S. Pat. No. 5,603,947. Other co-solvents, including hexane, have been suggested for use with silicone adhesives used in transdermal devices. See p. 3, line 51, et seq. of EPO 524776 A1.

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Mecamylamine is an antagonist to nicotine. U.S. Patent Nos. 5,316,759, 5,726,190, and 5,574,052 teach the coadministration of mecamylamine and nicotine to treat nicotine dependency. These patents do not teach or suggest the transdermal administration of mecamylamine itself to treat nicotine dependency. Furthermore, the prior art does not teach that coadministration of mecamylamine and nicotine is especially effective as a smoking cessation aid specifically suited for women.

DISCLOSURE OF THE INVENTION

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One aspect of this invention is a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

- a) a top backing layer that is impermeable to the drug;
- b) silicone adhesive layer containing the drug and underlying the backing layer;
- c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and
- d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and the acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

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Another aspect of the invention is a method of making a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

- a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;
- b) evaporating the hexane from the coating to form a silicone adhesive layer containing the drug; and

c) laminating a polyacrylate adhesive layer affixed to a release liner layer onto the silicone adhesive layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

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Another aspect of the invention is a method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal coadministration (or other coadministration except by smoking) of nicotine to the person.

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A further aspect of the invention is a method for treating a woman for nicotine dependence comprising transdermally coadministering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine.

BRIEF DESCRIPTION OF THE DRAWINGS

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Figure 1 is a elevational cross-sectional view of an embodiment of the invention patch.

Figures 2-6 are graphs of the results of the *in vitro* skin flux tests described in the examples.

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Figures 7 and 8 are graphs of the results of the clinical studies described in the examples.

MODES FOR CARRYING OUT THE INVENTION

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As used herein the term "volatile liquid drug" intends a drug that (i) is capable of permeating through unbroken human skin at therapeutically effective rates from a patch of practical size, the permeation either being unenhanced or enhanced through coadministration of one or more skin permeation enhancing agents, (ii) is a liquid at 25°C, atmospheric pressure, and (iii) has a boiling point less than about 300°C at atmospheric pressure. Examples of such drugs are nicotine, mecamylamine, selegiline, and nitroglycerine.

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As used herein the term "diffusional contact" intends a relationship, either through direct contact or through indirect contact via an intermediary material, between two surfaces or layers such that drug is able to pass by diffusion from one surface or layer to the other surface or layer.

As used herein the term "treating a person for nicotine dependence" intends causing the person to reduce or eliminate his or her intake of nicotine from smoking and/or chewing tobacco on a temporary or permanent basis.

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The embodiment of the invention shown in Figure 1 is a four-layer laminated composite matrix type transdermal patch, generally designated 10. The four layers are: (1) a top drug-impermeable backing layer 11; (2) an intermediate drug-containing silicone adhesive layer 12; (3) a basal drug-containing polyacrylic adhesive layer 13; and (4) a removable release liner layer 14.

Materials for making backing layer 11 are well known in the art. They include various polymers such as polyethylene terephthalate, polyethylene, polypropylene and polyvinyl chloride, metal foils such as aluminum foil, and polymer-metal composites.

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Adhesive layer 12 is made from a pressure sensitive silicone adhesive. An amine compatible silicone adhesive is preferred for use with drugs, such as nicotine, which contain amine groups. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). See also Pfister, W.R., et al. "Silicon Adhesives for Transdermal Drug Delivery" Chemistry in Britain (Jan. 1991), pp. 43-46 and EP Pub. No. 0524776 A1. Suitable commercially available silicone pressure sensitive adhesives are available from Dow Corning under the trademark BIO-PSA. The silicone pressure sensitive adhesives are supplied commercially as solutions in a solvent. Per the present invention the solvent should be hexane. The thickness of layer 12 will usually be in the range of about 25 to 100 microns, more usually 50 to 75 microns. Expressed alternatively, the layer 12 will be present at about 4 to 18 mg/cm², more usually 8 to 14 mg/cm². Adhesive layer 12 initially (before it is laminated to adhesive layer 13) contains the entire drug loading. In this regard, the drug(s) will usually be added to the silicone adhesive in amounts ranging between about 5% to 50% by weight, more usually 10% to 30% by weight, based on the total dry weight of drug and adhesive.

Adhesive layer 13 is made from one or more solution acrylic pressure sensitive adhesives. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 396-456 (D. Satas, ed.) Van Nostrand Reinhold, New

York (1989). They are usually copolymers composed of: 50% to 90% of a main acrylate or methacrylate monomer, usually 2-ethylhexyl acrylate, butylacrylate, or iso-octyl acrylate: 10% to 40% of a modifying monomer such as vinyl acetate; and 2% to 20% of a functional group-containing monomer such as acrylic acid. Examples of suitable commercially available solution acrylic pressure sensitive adhesives are: National Starch DuroTak® adhesives 87-2194 and 87-2070. The thickness of the acrylic adhesive layer 13 will usually be about the same as that of layer 12. After lamination to the silicone adhesive layer 12 and equilibration of the drug between layers 12 and 13, layer 13 will also contain drug. In this regard the drug will usually constitute about 2.5% to 30% by weight, preferably 5% to 15% by weight, of layer 13 after equilibration occurs.

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The release liner layer 14 is removed before device 10 is placed on the skin. After layer 14 is removed the lower surface of layer 13 is exposed and defines the basal surface of the device which is intended to be placed directly in contact with the skin. Release liner layers are well known in the transdermal patch art. They are made of materials that permit the layer to be easily stripped or peeled away from the adjacent pressure sensitive adhesive layer. Release liner layers are typically made from drug impermeable polymers such as polyesters which are coated with materials such as silicone or fluorinated hydrocarbons that reduce the adhesiveness between it and the adjacent pressure sensitive adhesive layer. In this regard since the acrylic pressure sensitive adhesive layer rather than the silicone pressure sensitive adhesive layer defines the basal surface of the device it is possible to use a siliconized release liner. Such liners are generally not compatible with silicone adhesives. Siliconized liners are more economical than fluorocarbon coated liners. Further, use of the acrylic pressure sensitive adhesive as the basal layer provides a more controlled and predetermined delivery of the drug than could be achieved using a silicone adhesive basal layer. The particular drug release profile from the patch can be varied by altering the thickness and/or composition of the acrylic pressure sensitive adhesive layer and/or the drug loading, and/or by employing a permeation enhancer.

The drug is released from the surface of the acrylic pressure sensitive adhesive to the skin at a therapeutically effective rate. That rate will depend upon the particular drug. In the case of nicotine, the rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr. In the case of co-administration of nicotine and the mecamylamine, the nicotine rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr, and the mecamylamine rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of

mecamylamine alone, the rate will usually be in the range of 0.02 to 1 mg/hr. preferably 0.1 to 0.6 mg/hr. In the case of selegiline, the rate will usually be in the range of 0.2 to 3 mg/day. The flux (rate per unit area) of drug from the basal surface of the acrylic pressure sensitive adhesive and the area of that surface are matched to provide the desired rate of drug administration. As indicated, the flux may be varied by altering the drug loading, composition and/or thickness of the acrylic pressure sensitive adhesive layer, and/or by the use of permeation enhancers. The surface area of the layer in diffusional contact with the skin will usually be in the range of 5 to 100 cm^2 , more usually in the range of about 10 to 50 cm². Each patch may be applied to the skin for periods of from several hours up to about a week, and more preferably for about 1 to 3 days.

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The patches of the invention are made in the following manner. The drug(s) is dissolved in the desired proportion(s) in a hexane solution of the pressure sensitive silicone adhesive. The drug(s) will normally constitute about 2.5% to 25% by weight of the solution. This solution is then cast onto the backing layer and allowed to dry. By casting the drug and silicone adhesive from a hexane solution, very low casting and drying temperatures (30°C to 40°C) may be used, thus reducing degradation or loss of the liquid drug(s) during the casting and drying process. Even though low processing temperatures in the 30°C to 40°C range are used, low residual hexane levels (e.g., < 0.1 % by wt.) are found in the layer after about 1 to 5 min. of drying. Other solvents, such as heptane and toluene, are not suitable since they require higher processing temperatures and thus result in more drug degradation and/or evaporation during coating and drying. Other pressure sensitive adhesives such as acrylics or polyisobutylenes are similarly not suitable for formulating liquid drugs since they require higher processing temperatures to remove their solvents (e.g., ethyl acetate, heptane, etc.). The silicone adhesive also has excellent adhesion to the backing. A solution of the acrylic pressure sensitive adhesive is cast onto a siliconized release liner layer and permitted to dry. The acrylic pressure sensitive adhesive/release liner subassembly is then laminated to the drug-containing silicone pressure sensitive adhesive/backing subassembly to form the final laminated composite. After lamination the drug(s) equilibrates in the adjacent adhesive layers. Patches are cut/punched from the composite and placed in appropriate packaging.

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Alternatively, the drug and silicone adhesive solution can be cast onto a disposable liner and dried as described. The sub-assembly can be laminated to the acrylic pressure sensitive adhesive/release liner subassembly. The disposable liner is then removed to expose the top surface of the silicone adhesive layer. A backing is then laminated to the top surface of the

silicone adhesive layer to form the final laminated composite. In still another alternative manufacturing scheme, the solution of silicone adhesive and drug is cast directly into the acrylic pressure sensitive adhesive release liner subassembly and dried. A backing is then applied to form the completed laminated composite.

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It has surprisingly been found that, in the treatment of nicotine dependence, women respond more favorably to a patch that combines nicotine and mecamylamine than to a patch that contains either nicotine or mecamylamine alone. The patch can be administered while the woman continues to smoke and then ceases smoking or if she chooses to stop smoking at the same time as beginning treatment.

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For treatment of nicotine dependence, the patches of the invention are typically worn for a total period of about 3 to 16 weeks. During the first 1 to 4 weeks, preferably 2 to 3 weeks, the patent is allowed to smoke as desired. During the remainder of the treatment, i.e., two to 12 weeks, preferably 4 to 8 weeks, the patient is advised to not smoke.

EXAMPLES

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The following examples further illustrate the patches of the invention and the process used to make them. These examples are not intended to limit the invention in any manner.

Example 1: Preparation and Testing of Nicotine Patch

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Nicotine was added to a hexane solution of Dow Corning BIO-PSA amine-compatible silicone pressure sensitive adhesive to a level of approximately 12% by weight based on the combined dry weight of adhesive and nicotine. The resulting hexane solution of adhesive and nicotine was coated onto a 3M Scotchpak 1109 polyester/polyolefin backing at 13.8 mg/cm² (1.63 mg/cm² nicotine and 12.17 mg/cm² adhesive) and the coated backing was dried at 30°C to 40°C for about 3 min.

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National Starch DuroTak 87 2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coater Products 1-5 PESTR (Matte) - 164Z siliconized polyester release liner at 13.18 mg/cm² and the coated release liner was dried at 100°C for about 10 min.

The dried silicone adhesive/nicotine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the nicotine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of nicotine within the layers was about 6% (w/w) after equilibration.

In vitro nicotine flux from the laminated composite was determined at 32°C through human cadaver epidermis into an infinite sink using modified Franz glass diffusion cells. Nicotine assays were made by HPLC.

For comparison purposes the flux of nicotine from commercial Habitrol3 21 mg/day patches was determined using the same test procedure. Figure 2 is a graph of the nicotine flux from the composite of the example and from the Habitrol3 patches versus time.

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Example 2: Preparation and Testing of Nicotine/Mecamylamine Patches
Nicotine and mecamylamine were added to a hexane solution of Dow Corning BIO-PSA
amine compatible silicone pressure sensitive adhesive. Two batches were made: one contained
approximately 10% nicotine and 6.4% mecamylamine based on the total dry weight of the
adhesive and the two drugs; and a second contained approximately 10% nicotine and 4.2%
mecamylamine, based on the total dry weight of the adhesive and the two drugs. The batches
were separately coated onto a 3M Scotchpak 1109 polyester/polyoefin backing fifth at 9.6
mg/cm² (0.96 mg/cm² nicotine, 0.61 mg/cm² mecamylamine, 8.03 mg/cm² adhesive for the first
batch; 0.96 mg/cm² nicotine, 0.40 mg/cm² mecamylamine, 8.24 mg/cm² adhesive for the second
batch) and then dried at 30 to 40°C for about 2 min.

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A blend of two National Starch DuroTak acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated at 8.0 mg/cm² onto a 75 micron thick Daubert Coater Products siliconized polyester release liner (1-3 PESTR (Matte) - 164Z) and dried at about 100°C for about 10 min.

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The drug-containing silicone adhesive/backing subassembly was then laminated to the acrylic adhesive/release liner subassembly to form a four layer/laminated composite. After lamination the nicotine and mecamylamine distributed themselves uniformly within the adjacent

adhesive layers. The concentration of the drugs in the adhesive layers after equilibration was: nicotine. 5.45% (w/w) and mecamylamine 3.47% (w/w) for the composite made from the first batch and 5.45% (w/w) and 2.27% (w/w), respectively, for the composite made from the second batch. Patches about 23 cm² in area were cut from the composites. These patches were designed to deliver 21 mg of nicotine and 6 mg of mecamylamine in 24 hr and 21 mg of nicotine and 3 mg of mecamylamine in 24 hr, respectively.

Nicotine and mecamylamine fluxes from the patches were determined using the procedure described Example 1. Mecamylamine assays were made by GC. Figure 3 is a graph showing the nicotine flux from the patches versus time. Patches made from the first batch composite are designated 21/6; those from the second batch composite are designated 21/3. Figure 4 similarly is a graph showing the mecamylamine flux from the patches.

Example 3 Preparation and Testing of Selegiline Patch

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Selegiline was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 10% by weight based on the combined dry weight of adhesive and selegiline. The resulting hexane solution of adhesive and selegiline was coated on 3M Scotchpak 1109 polyester/polyolefin backing at 10.0 mg/cm² (1.0 mg/cm² selegiline and 9.0 mg/cm² adhesive) and the coated backing was dried at 30°C to 40°C for about 3 minutes.

National Starch DuroTak® 87-2194 acrylic solution pressure sensitive achesive was coated onto a 125 micron thick Daubert Coated Products 1-5 PESTER (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm² and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/selegiline-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the selegiline distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of selegiline within the layers in about 5.5% (w/w) after equilibration.

Selegiline flux from the patches was determined using the procedure described in Example 1. Selegiline assays were made by HPLC.

Figure 5 is a graph of the selegiline flux from the composite of this example versus time.

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Example 4. Preparation and Testing of Mecamylamine Patch

Mecamylamine was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 6.3% by weight based on the combined dry weight of adhesive and mecamylamine. The resulting hexane solution of adhesive and mecamylamine was coated on 3M Scotchpack 1109 polyester/polyolefin backing at 9.6 mg/cm² (0.61 mg/cm² mecamylamine and 8.99 mg/cm² adhesive) and the coating backed was dried at 30°C to 40°C for about 3 minutes.

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A blend of two National Starch DuroTak® acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w. respectively, was made. The blend was coated onto a 75 micron thick Daubert Coated Products 1-2 PESTR (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm² and the coated release liner was dried at about 100°C for about 10 minutes.

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The dried silicone adhesive/mecamylamine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner sübassembly to form a four-layer laminated composite. Following lamination, the mecamylamine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of mecamylamine within the layers is about 3.47% (w/w) after equilibration. Patches about 23 cm² in area were cut from the composites. These patches were designed to deliver 6 mg of mecamylamine in 24 hr.

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Mecamylamine flux from the patches was determined using the procedure described in Example 1. The mecamylamine assay was done by gas chromotography. Figure 6 is a graph of the mecamylamine flux from the composite of this example versus time; mecamylamine flux through the same section of cadaver skin from the 21/3 and 21/6 compositions of Example 2 are shown for comparison.

Study A.

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Patches made according to Examples 1, 2 and 4 and a placebo patch were subject to a clinical study. The study was a multi-center, double-blind, randomized parallel group study. Patients were randomized to receive one of five treatments: nicotine/mecamylamine 21/6: nicotine/mecamylamine 21/3; nicotine (21 mg/24 hr); mecamylamine (6 mg/24 hr) and placebo. Patches were applied daily for the first six weeks of the study. Patients were instructed to continue smoking for the first two weeks and to stop smoking thereafter.

Among the efficacy parameters monitored during the study were four week continuous abstinence after the quit smoking date, nicotine plasma concentration, and ad hoc smoking during the treatment period.

Table 1 below provides the overall abstinence data for the study. In the table "N" represents the number of patients, "No" indicates non-abstinence and "Yes" indicates abstinence. As indicated the nicotine/mecamylamine 21/6 gave the highest abstinence.

Table 1

	Overall	21/6	21/3	21/0	0/6	Pla
N	705	142	141	141	140	141
No	82%	74%	79%	79%	82%	92%
Yes	18%	26%	21%	21%	18%	8%

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Figure 7 is a graph showing the mean nicotine plasma concentrations in ng/ml of the patients by treatment and time. As shown, the mecamylamine only patch (0/6) produced a steady decline in nicotine levels even during the initial two-week period of the study. Fig. 8 is a graph showing the mean observed change in the number of cigarettes smoked by treatment and day. Surprisingly, the number of cigarettes smoked did not increase with the mecamylamine only (0/6) treatment, as the literature reports that oral mecamylamine administration increased ad hoc cigarette consumption.

Study B.

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A second multi-center, double-blind, randomized parallel group clinical study was conducted. Patients were randomized to receive one of three treatments: nicotine/mecamylamine 21/6; nicotine/mecamylamine 21/3, and nicotine (21 mg/24 hr). Patient instructions were the same as in the first study.

The abstinence data for this study are summarized in Table 2. In this study the nicotine/mecamylamine combination was again more effective than nicotine alone.

10 Table 2

Treatment	21/6	21/3	21/0
N	180	180	180
Abstinence	29%	29%	23%

A detailed examination of the data the clinical studies yielded a surprising difference in abstinence rates for females and males. In both studies, the abstinence rate for females in the 21/6 treatment group was 31% compared to the 21/0 treatment group rates of 17% in the first study and 18% in the second study. These gender specific data are summarized in Table 3.

Table 3

Study	Gender		21/6	21/3	21/0	0.6	Plac
First	Female	N	70	67	63	75	74
		% Abst.	31	16	17	17	9
	Male	N	72	74	78	65	67
		% Abst.	21	26	24	18	6
Second	Female	N	93	96	91		
		% Abst.	31	29	18		
	Male	N	87	84	89		
		% Abst.	28	29	28		

N = number of subjects in study.

5 % Abst.= Four-week continuous abstinence results.

Modifications of the above described modes for carrying out the invention that are obvious to persons of skill in the transdermal patch art are intended to be within the scope of the following claims. All publications, patent applications and patents noted above are hereby incorporated by reference.

CLAIMS

1. A transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) a top backing layer that is impermeable to the drug:

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- b) an intermediate silicone adhesive layer containing the drug and underlying the backing layer;
- c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and
- d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.
- 2. The transdermal patch of claim 1, wherein the drug is nicotine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour to the patient.
- 3. The transdermal patch of claim 1, wherein the drug is a combination of nicotine and mecamylamine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour and 0.02 to 1 mg mecamylamine per hour to the patient.
- 4. The transdermal patch of claim 1 wherein the drug is selegiline and the patch is capable of administering 0.2 to 3 mg selegiline per day to the patient.
- 5. The patch of claim 1 wherein the drug is mecamylamine only and the patch is capable of administering 0.02 to 1 mg mecamylamine per hour to the patient.
 - 6. The patch of claim 1 wherein the release liner layer is a siliconized release liner layer.
- 7. The patch of claim 1 wherein the acrylic adhesive layer is made from a blend of two acrylic adhesives.

8. A method of making a transdermal patch for administering a volatile liquid drug to a patient comprising:

- a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;
- b) evaporating the hexane from the coating to form a layer of drug-containing silicone adhesive on the backing layer; and
- c) laminating an assembly comprising an acrylic adhesive coated onto a release liner layer onto the silicone adhesive layer on the backing layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.
 - 9. The method of claim 8 wherein step b) is carried out at 30°C to 40°C.
- 10. The method of claim 8 wherein the release liner layer is a siliconized release liner layer.
 - 11. The method of claim 8 wherein the drug is nicotine.

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- 12. The method of claim 8 wherein the drug is a combination of nicotine and mecamylamine.
 - 13. The method of claim 8 wherein the drug is selegiline.
 - 14. The method of claim 8 wherein the drug is mecamylamine only.
- 25 15. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal coadministration of nicotine to the person.
- 16. The method of claim 15 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr.
 - 17. The method of claim 15 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr.

18. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine to the person for a first time period during which the person smokes cigarettes as desired and continuing said administration for a second time period during which the person is advised to not smoke.

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19. The method of claim 18 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.

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- 20. The method of claim 18 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.
- 21. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman.

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22. The method of claim 21 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr and the rate of nicotine administration is 0.2 to 1.5 mg/hr.

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23. The method of claim 21 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr and the rate of nicotine administration is 0.3 to 0.9 mg/hr.

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24. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman for a first time period during which the woman smokes cigarettes as desired and continuing said administration for a second time period during which the woman is advised to not smoke

25. The method of claim 24 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.

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26. The method of claim 24 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.

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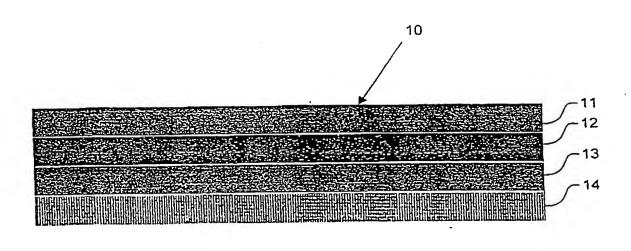
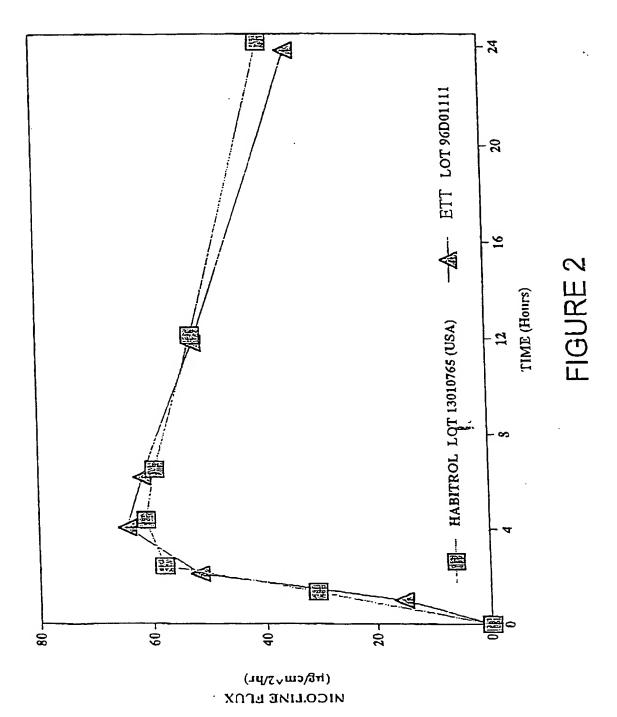
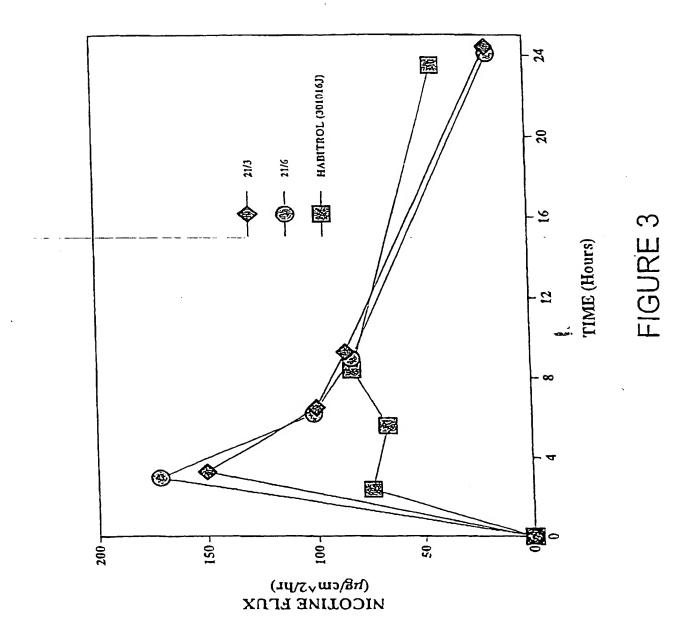
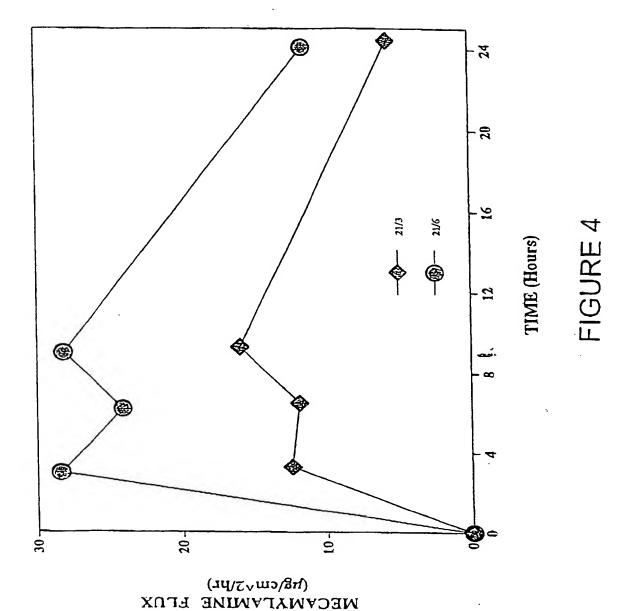


FIGURE 1

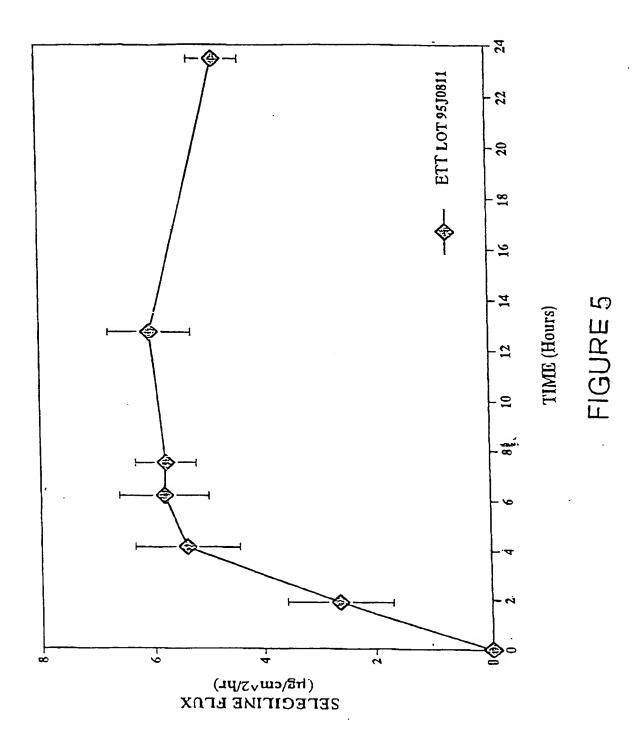
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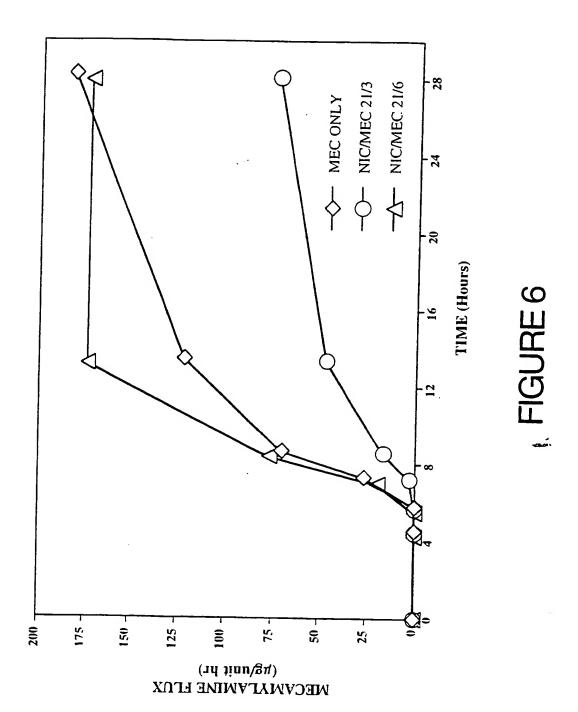


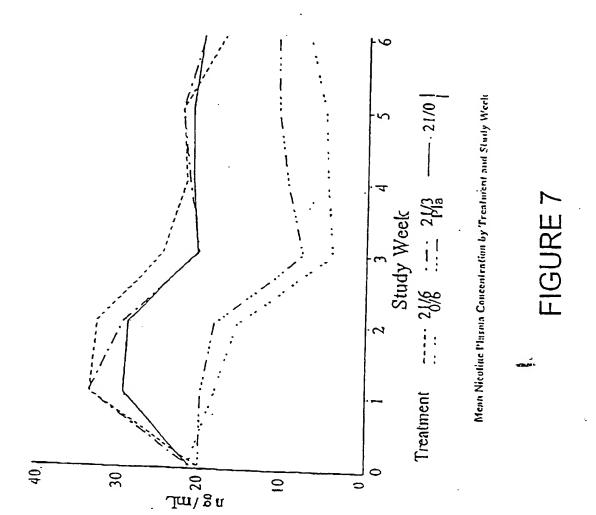


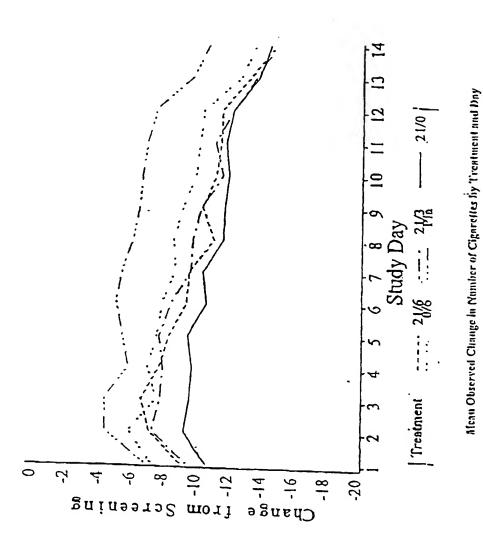


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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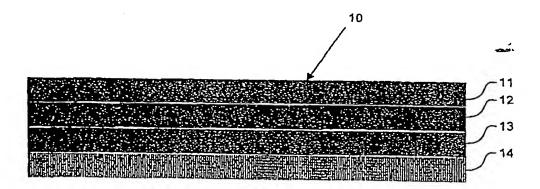
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(57) Abstract

A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

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EE	Estonia	LR	Liberia	SG			
			2.0cm	36	Singapore		

INTERNATIONAL SEARCH REPORT

Inc. .ational Application No PCT/US 99/28697

A. CLASSIFICATION OF SUBJECT MATTER

A61K9/70,A61K31/465,A61K31/137,A61K31/131,C07D401/04, C07C211/27,C07C211/36

According to International Patent Clambication (IPC) or to both national clambication and IPC 7

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched . . .

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Calegory *	Citation of document, with indication, where appropriate, of the relevant passages	- Relevant to claim No.
x	WO 96/40085 A (NOVEN PHARMACEUTICALS, INC.) 19 December 1996, page 8, line 14 - page 9, page 18, line 32 - page 19, line 2, page 19, lines 18-37, examples 2-4, claims 1,3-6, 9,10,17,19-21,24.	1,2, 4,6-8, 10,11, 13
Y		3,5
x	WO 93/00058 A (NOVEN PHARMACEUTICALS, INC.) 07 January 1993, page 24, line 9, claims 1-5, 14-19,37-39,53-64,91-93.	1,2, 4,6
Y	14 15,5, 55,55 O4,51 55.	3,5
Y	US 4717568 A (ECKENHOFF ET AL.)	3,5

X Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
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INTERNATIONAL SEARCH REPORT

Interr 'nal Application No

Cakgory *	Acion) DOCUMENTS CONSIDERED TO BE RELEVANT	
-ac gory	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
×	05 January 1988, abstract, column 18, lines 25,26. US 5691365 A (CROOKS ET AL.) 25 November 1997, abstract, column 4, lines 20-29, column 14, lines 50-67, column 16, line 63.	15-20
c	US 5316759 A (ROSE ET AL.) 31 May 1994, abstract, claims.	21-26
A	US 5230898 A (HORSTMANN ET AL.) 27 July 1993, the whole document.	1-26
Α.	US 5176915 A (HOFFMANN) 05 January 1993, the whole document.	1-26
		- Canada

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

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	Im Recherchenbericht		harchanharist*	T	de l' Office.					
	angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche		Patentdokumente document cited earch report nt de brevet cité	Datum der Veröffentlichung Publication date Date de publication		Pat Pat ma Mem	ilied(er) der tentfamilie lent family ent family bre(s) de la e de brevets	Datum der Veröffentlichung Publication date Date de publication		
	WO	A2	9640085	19-12-1996	AU					
1	WO	A3	9640085	13-03-1997	CA		60289/96	30-12-1996		
1					EP	A2	2223588 833671	19-12-1996		
					IL	A0	122484	08-04-1998		
					JP	T2	11506744	15-06-1998		
	WO	Al	9300058	07-01-1993	AU	A1	22689/92	15-06-1999		
					UA	B2	670033	25-01-1993		
					BR	A	9206208	04-07-1996		
					CA	AA	2110914	22-11-1994		
1					EP	Al	591432	07-01-1993		
1					EP	A4	591432	13-04-1994		
					FI	A	935833	17-05-1995		
1					FI	A0	935833	23-12-1993		
1					IL	A0	102277	23-12-1993 14-01-1993		
1					JР	Т2	6510279	17-11-1994		
1					MX	Al	9203648	31-01-1995		
1					ИО	A0	934523	10-12-1993		
]					NO	Α	934523	10-02-1994		
ĺ					NZ	Α	243200	25-11-1993		
+					SG	A1	49164	18-05-1998		
1					US	Α	5474783	12-12-1995		
l					US	Α	5958446	28-09-1999		
					US	Α	5656286	12-08-1997		
]					US	Α	6024976	15-02-2000		
1					ZA	A	9209992	23-06-1994		
					ΑT	E	99176	15-01-1994		
					AU	Al	32847/89	22-09-1989		
ļ					UA	B2	606840	14-02-1991		
					CA	A1	1338660	22-10-1996		
					DE DE	C0 T2	68911920	10-02-1994		
					DK	A0	68911920	07-07-1994		
					DK	A	5494/89 5494/89	03-11-1989		
					EP	A1	418248	29-11-1989		
					EP	B1	418248	27-03-1991		
					FI	A0	904358	29-12-1993		
					НK	A1	1006285	04-09-1990		
					JP	Т2	3503283	19-02-1999		
					JР	B2	2659837	25-07-1991 30-09-1997		
					KR	Bl	9513461	08-11-1995		
					US	Α	4814168	21-03-1989		
					WO	Al	8907950	08-09-1989		
					US	А	4994278	19-02-1991		
					บร	А	4994267	19-02-1991		
					US	Α	5032207	16-07-1991		
					US	А	5300291	05-04-1994		
					บร	Α	5405486	11-04-1995		
					US	А	5656285	12-08-1997		
-					US	A	5686099	11-11-1997		

For more details about this annex see Official Journal of the European Patent Office, No. 12/82.

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PCT/US 99/28697 SAE 268121

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In Deskins to the second				de l' Offic	t n'engagent pas la responsibilit e.
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets			Datum der Veröffentlichung Publication date Date de publication
		US	A	5719197	17-02-1998
		AT	E	122240	15-05-1995
		ΑU	Al	50349/90	13-08-1990
		ΑU	B2	632534	07-01-1993
		CA	AA	2044132	12-07-1990
		CA	С	2044132	06-05-1997
		DE	C0	69019175	14-06-1995
		DE	Т2	69019175	18-01-1996
		DK	Т3	379045	09-10-1995
		EP	A1	379045	25-07-1990
		EP	Al	453505	30-10-1991
		EP	Al	634179	18-01-1995
		EP	B1	379045	10-05-1995
		ES	Т3	2071683	01-07-1995
		HK	A1	1006155	12-02-1999
		ΙE	В	69048	07-08-1996
		JP	Т2	4502719	21-05-1992
		JP	B4	7093939	11-10-1995
		ИL	А	9020159	02-01-1991
		PT	Α	92830	31-07-1990
		PT	В	92830	29-12-1995
		WO	A1	9007940	26-07-1990
		ΑU	A1	54206/90	21-10-1991
		BR	Α	9008012	01-12-1992
		DK	Т3	474647	18-08-1997
		EP	B1	474647	05-02-1997
		FI	Α	924313	25-09-1992
		FI	A0	924313	25-09-1992
		WO	A1	9114463	03-10-1991
		DE	CO	69029909	20-03-1997
		DE	Т2	69029909	11-09-1997
		EP	A1	474647	18-03-1992
		ИО	A0	923699	24-09-1992
		NO	А	923699	01-02-1993
		ΑU	A1	15212/95	01-08-1995
		ΑU	B2	700429	07-01-1999
		BR	A	9506470	07-10-1997
		CA	AA	2180530	13-07-1995
		CN	Α	1143318	19-02-1997
		EP	A1	737066	16-10-1996
		FI	A0	962770	05-07-1996
		FI	Α	962770	29-08-1996
		HU	A0	9601856	30-09-1996
		HU	A2	74913	28-03-1997
		IL	A0	112269	30-03-1995
		JP	T2	9511987	02-12-1997
		МО	A0	962833	05-07-1996
		МО	A	962833	15-08-1996
		NZ	А	278769	27-04-1998

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

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To the International Search Report to the international Patent Application No. Au rapport de recherche international relativ à la demande de brevet international n°

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	de l' Office.					
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication		Pate Pate me Memb	ied(er) der entfamilie ent family mber(s) ore(s) de la de brevets	Datum der Veröffentlichung Publication date Date de publication	
		SG	A1	49331	18-05-1998	
		WO	A1	9518603	13-07-1995	
		ZA	A	9500108	25-03-1996	
		CA	AA	2025033	16-03-1991	
		ΑU	A1	20040/92	21-12-1992	
		CA	AA	2109099	26-10-1992	
		EP	A1	592481	20-04-1994	
		SG	A1	43349	17-10-1997	
		WO	A1	9219451	12-11-1992	
		CA	AA	2126366	22-12-1994	
		AΤ	E	144704	15-11-1996	
		ΑU	Al	14610/92	06-10-1992	
		UA	B2	658870	04-05-1995	
		υA	A1	28331/95	28-09-1995	
		ΑU	B2	694243	16-07-1998	
		CA	AA	2104474	28-08-1992	
		DE	C0	69214938	05-12-1996	
		DE	T2	69214938	15-05-1997	
		DK	Т3	573576	01-04-1997	
		EP	A1	573576	15-12-1993	
		EP	A2	728477	28-08-1996	
		EP	A3	728477	11-09-1996	
		EP	B1	573576	30-10-1996	
		ES	т3	2094906	01-02-1997	
		FI	A	933761	26 <u>-0</u> 8-1993	
		FI	0A	933761	26-08-1993	
		GR	Т3	3022708	31-05-1997	
		JP	Т2	6508820	06-10-1994	
		МО	A0	933296	16-09-1993	
		NO	A	933296	01-11-1993	
		МО	B1	307363	27-03-2000	
		SG	A1	49158	18-05-1998	
		WO	A1	9215289	17-09-1992	
		US	A	5234957	10-08-1993	
		US US	A	5332576	26-07-1994	
		AU	A	5446070	29-08-1995	
		CA	A1	76722/94	21-03-1995	
		WO	AA	2170504	02-03-1995	
		WO	Al Al	9505813 9640084	02-03-1995	
		wo	A1	9606602	19-12-1996	
		AU	A1	60290/96	07-03-1996	
		WO	A2	9640086	30-12-1996	
		wo	A2 A3	9640086	19-12-1996	
		ZA	A	9604735	13-02-1997	
		AT	E	148633	19-12-1996	
		ES	T3	2097145	15-02-1997	
			د ن	2021143	01-04-1997	
		ΑU	A1	34168/95	22-03-1996	

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

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PCT/US 99/28697 SAE 268121

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	Im Recherchenbericht Datum der				de l' Office.						
	angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche		Datum der Veröffentlichung Publication date Date de publication		Pa Pa m Men	glied(er) der stentfamilie stent family sember(s) sbre(s) de la	Datum der Veröffentlichung Publication date Date de				
	US A 4717			<u> </u>		le de brevets	publication				
		300	05-01-1988	AU			26-09-1985				
				AU			14-04-1988				
i				BE			01-07-1985				
				CA		,	12-05-1987				
	•			DE	A1	3509410	26-09-1985				
				DE	C2	3509410	20-03-1997				
1				ES	A1	540185	16-11-1985				
-				ES	A5	540185	16-12-1985				
-				ES	Al	8602388	16-03-1986				
1				FR FR	Al	2561103	20-09-1985				
1				GB	B1	2561103	07-04-1989				
1				GB	A0 A1	8431661	30-01-1985				
1				GB	B2	2155787	02-10-1985				
1				IT	A0	2155787	16-12-1987				
				IT	A	8567263 1185795	18-03-1985				
1				JP	A2	60236665	18-11-1987				
1				JP	B4	6041406	25-11-1985				
1				MX	A.	161579	01-06-1994				
j				NL	A	8500697	12-11-1990				
1				NZ	A	210601	16-10-1985				
1				US	A	4595583	08-01-1988				
]				ZA	A	8409802	17-06-1986				
				US	Α	4612186	28-08-1985				
]				US	Α	4624945	16-09-1986 25-11-1986				
1				US	A	4684524	04-08-1987				
l				US	A	4692336	08-09-1987				
		•		US	Α	4717566	05-01-1988				
1				US	A	4717718	05-01-1988				
				US	A	4729793	08-03-1988				
				US	A	4772474	20-09-1988				
				US	A	4844984	04-07-1989				
				US	A	4927633	22-05-1990				
				US	A	5000957	19-03-1991				
				AR	Al	240399	30-04-1990				
				AU AU	A1	60697/86	12-02-1987				
				BE	B2	591511	07-12-1989				
				BR	A1	905249	01-12-1986				
				CA	A Al	8603678	10-03-1987				
				DE	A1	1278968	15-01-1991				
				DE	C2	3625915	19-02-1987				
				ES	A1	3625915 556303	24-04-1997				
				ES	A5	556303	16-10-1987				
				ES	A1	8800042	16-11-1987				
				FR	Al	2585950	01-01-1988				
				FR	B1	2585950	13-02-1987				
				GB	A0	8618350	03-03-1989				
-				GB	Al	2178659	03-09-1986				
							18-02-1987				

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Diese Angaben dienen nur zur

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

In diesem Anhang sind die Mitglieder der This annex lists the patent family members Patentfamilien der im obengenannten relating to the patent documents cited in the above-mentioned search report.
The European Patent Office is in no way liable for these particulars which are merely internationalen Recherchenbericht angeführten Patentdokumente angegeben. Unterrichtung und erfolgen ohne Gewähr. given for the purpose of information.

La presente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité. de l' Office.

Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche			Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets			Datum der Veröffentlichung Publication date Date de publication
			<u>' </u>	GB	B2	2178659	13-09-1989
				IT	A0	8667641	07-08-1986
				IT	A	1195818	27-10-1988
		_		JР	A2	62039518	20-02-1987
		••		JP	B4	8018972	28-02-1996
				NL	A.	8601971	02-03-1987
				NZ	A	216991	27-09-1989
				ZA	A	8605914	29-04-1987
US	A	5691365	25-11-1997			none	29-04-1987
US	A	5316759	31-05-1994	US	A	5574052	12 11 1006
				US	A	5703101	12-11-1996 30-12-1997
				US	A	5726190	
				US	A	5861422	10-03-1998
				บร	A	5935975	19-01-1999
				US	A	4846199	10-08-1999
				บร	A	4945928	11-07-1989
US	Α	5230898	27-07-1993	TA	E	88911	07-08-1990
			2. 0. 1999	ΔI	A1	51314/90	15-05-1993
				AU	B2	627283	04-10-1990
				CA	AA	2013050	20-08-1992
				CA	C	2013050	01-10-1990
				CS	A2	9001483	28-04-1998
				CZ	B6	284287	15-10-1991
				DD	A5	293266	14-10-1998
				DE	Al	3910543	29-08-1991
				DE	C2	3910543	11 <u>-</u> 10-1990 07-01-1993
				DE	C0	59001338	09-06-1993
				DK	т3	391172	27-09-1993
				EP	Al	391172	10-10-1990
				EP	B1	391172	05-05-1993
				ES	T3	2055201	16-08-1994
				FI	A0	901556	28-03-1990
				FI	B1	103478	15-07-1999
				HR	A1	930590	30-04-1995
				HR	Bl	930590	31-10-1997
				HU	A0	902018	28-08-1990
				HU	A2	54062	28-01-1991
				НU	В	205254	28-04-1992
				ΙE	В	65520	01-11-1995
				IL	A0	93956	23-12-1990
				IL	A1	93956	31-12-1995
				JP	A2	3027311	05-02-1991
				JP	В2	2552191	06-11-1996
				KR	B1	9607517	05-06-1996
				NO	A0	901458	30-03-1990
				NO	A	901458	02-10-1990
				NO	В	180671	17-02-1997
				NO	c	180671	28-05-1997
				NZ	A	233152	23-12-1991

Zum internationalen Recherchenbe-richt über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

ANNEX

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PCT/US 99/28697 SAE 268121

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Au rapport de recherche inter-national relativ à la demande de brevet international n°

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	T	de l' Office.				
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de ta famille de brevets			Datum der Veröffentlichung Publication date Date de publication	
		PL	Bl	163297	31-03-1994	
		PT	Α	93621	08-01-1991	
		PT	В	93621	28-06-1996	
		SI	Α	9010635	30-06-1998	
		បន	Α	5702721	30-12-1997	
		YU	Α	635/90	31-10-1991	
		ZA	A	9002465	30-01-1991	
US A 5176915	05-01-1993	ΑT	E	133569	15-02-1996	
		AU	Al	50766/90	01-11-1990	
		ΑU	B2	622775	16-04-1992	
		CA	AA	2012124	15-09-1990	
		CZ	A3	9001137	17-11-1999	
		DD	A5	296844	19-12-1991	
		DE	A1	3908432	27-09-1990	
		DE	C2	3908432	04-07-1991	
		DE	C0	59010095	14-03-1996	
		DK	Т3	387694	24-06-1996	
		EP	A2	387694	19-09-1990	
		EP	A3	387694	28-11-1990	
		EP	B1	387694	31-01-1996	
		ES	тЗ	2085293	01-06-1996	
		FI	A0	901291	15-03-1990	
		GR	Т3	3019786	31-07-1996	
		HR	A1	930666	31-10-1994	
		HR	B1	930666	31-08-1998	
		HU	A0	901423	28=06-1990	
		HU	A2	53814	28-12-1990	
		HU IE	В	206992	01-03-1993	
		IL	B A0	74681	30-07-1997	
		JP	AU A2	93679	23-12-1990	
		JP	B2	3014515	23-01-1991	
		KR	B1	2588039	05-03-1997	
		NO	A0	9513462 901127	08-11-1995	
		NO	A	901127	09-03-1990	
•		NZ	A	232896	17-09-1990	
		PH	A	26277	26-04-1991	
		PL	B1	162638	10-04-1992	
		PT	A	93431	31-12-1993	
		PT	В	93431	07-11-1990	
		SI	A	9010494	30-04-1996	
		ZA	A	9001940	30-06-1998	

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- (74) Agents: BEARD, Collen, A. et al.: Jones & Askew, LLP, 2400 Monarch Tower, 3424 Peachtree Road, N.E., Atlanta, GA 30326 (US).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW. SD, SL, SZ, TZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, Fl, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

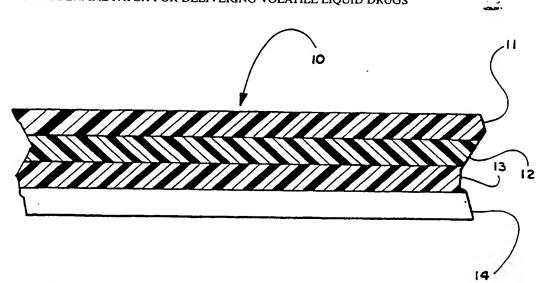
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(54) Title: TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS



(57) Abstract: A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

00/33812 A3



(15) Information about Correction: see PCT Gazette No. 17/2002 of 25 April 2002, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS

TECHNICAL FIELD

This invention is in the field of transdermal drug delivery devices. More particularly, it relates to a method for making transdermal patches that deliver volatile liquid drugs, such as nicotine, inecamylamine and selegiline, and to the resulting patches. The invention also relates to a method for treating a person for nicotine dependence comprising transdermally administering an effective amount of mecamylamine to the person without transdermal coadministration of nicotine. The invention further relates to a method for treating women for nicotine dependence comprising transdermally co-administering effective doses of mecamylamine and nicotine.

BACKGROUND ART

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There are two basic types of transdermal patches that are used to deliver liquid drugs. One is a liquid reservoir patch in which the liquid drug, either neat or dissolved in a carrier, is confined in a pouch or sac within the device. An example of such a device for delivering nicotine is shown in Fig. 1 of U.S. Pat. No. 5,364,630. The other is a matrix patch in which the liquid drug is dissolved in one or more polymeric layers of a laminated composite. Examples of matrix patches that deliver nicotine are described in U.S. Pat. No. 5,603,947. The present invention relates to a matrix patch.

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In the manufacture of matrix patches for administering volatile liquid drugs such as nicotine it is common to attempt to avoid steps involving heat treatment, e.g., drying, so as to avoid excessive loss or degradation of the drug. For instance U.S. Pat. No. 4,915,950 and 5,603,947 describe a printing procedure whereby neat nicotine is applied to a nonwoven fabric laminated to a polyisoburylene adhesive layer. Alternatively "hot" melt adhesives that melt at relatively low temperatures have been used as a matrix material for these drugs. See U.S. Pat. No. 5,411,739.

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PCT Pub. No. WO 96/40085 describes transdermal matrix patches for administering drugs such as selegiline. nitroglycerin and nicotine, that are liquid at normal room temperature. The publication suggests making a monolithic matrix of the drug in an adhesive by mixing one

or more polymeric adhesives, preferably polyacrylate and polysiloxane, and the drug in a volatile solvent, casting the mixture, and evaporating the solvent. The publication lists as examples of volatile solvents isopropanol, ethanol, xylene, toluene, hexane, cyclohexane, heptane, ethyl acetate and butyl acetate.

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When silicone adhesives have been used as the matrix material in nicotine patches the matrix layer has been cast from a heptane solution. See, for instance, Example 1 of U.S. Pat. No. 5,603,947. Other co-solvents, including hexane, have been suggested for use with silicone adhesives used in transdermal devices. See p. 3, line 51, et seq. of EPO 524776 A1.

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Mecamylamine is an antagonist to nicotine. U.S. Patent Nos. 5,316,759, 5,726,190, and 5,574,052 teach the coadministration of mecamylamine and nicotine to treat nicotine dependency. These patents do not teach or suggest the transdermal administration of mecamylamine itself to treat nicotine dependency. Furthermore, the prior art does not teach that coadministration of mecamylamine and nicotine is especially effective as a smoking cessation aid specifically suited for women.

DISCLOSURE OF THE INVENTION

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One aspect of this invention is a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

- a) a top backing layer that is impermeable to the drug;
- b) silicone adhesive layer containing the drug and underlying the backing layer;
- c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and
- d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and the acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

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Another aspect of the invention is a method of making a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

- a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;
- b) evaporating the hexane from the coating to form a silicone adhesive layer containing the drug; and

c) laminating a polyacrylate adhesive layer affixed to a release liner layer onto the silicone adhesive layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

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Another aspect of the invention is a method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal coadministration (or other coadministration except by smoking) of nicotine to the person.

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A further aspect of the invention is a method for treating a woman for nicotine dependence comprising transdermally coadministering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine.

BRIEF DESCRIPTION OF THE DRAWINGS

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Figure 1 is a elevational cross-sectional view of an embodiment of the invention patch.

Figures 2-6 are graphs of the results of the *in vitro* skin flux tests described in the examples.

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Figures 7 and 8 are graphs of the results of the clinical studies described in the examples.

MODES FOR CARRYING OUT THE INVENTION

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As used herein the term "volatile liquid drug" intends a drug that (i) is capable of permeating through unbroken human skin at therapeutically effective rates from a patch of practical size, the permeation either being unenhanced or enhanced through coadministration of one or more skin permeation enhancing agents, (ii) is a liquid at 25°C, atmospheric pressure, and (iii) has a boiling point less than about 300°C at atmospheric pressure. Examples of such drugs are nicotine, mecamylamine, selegiline, and nitroglycerine.

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As used herein the term "diffusional contact" intends a relationship, either through direct contact or through indirect contact via an intermediary material, between two surfaces or layers such that drug is able to pass by diffusion from one surface or layer to the other surface or layer.

As used herein the term "treating a person for nicotine dependence" intends causing the person to reduce or eliminate his or her intake of nicotine from smoking and/or chewing tobacco on a temporary or permanent basis.

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The embodiment of the invention shown in Figure 1 is a four-layer laminated composite matrix type transdermal patch, generally designated 10. The four layers are: (1) a top drug-impermeable backing layer 11; (2) an intermediate drug-containing silicone adhesive layer 12; (3) a basal drug-containing polyacrylic adhesive layer 13; and (4) a removable release liner layer 14.

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Materials for making backing layer 11 are well known in the art. They include various polymers such as polyethylene terephthalate, polyethylene, polypropylene and polyvinyl chloride, metal foils such as aluminum foil, and polymer-metal composites.

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Adhesive layer 12 is made from a pressure sensitive silicone adhesive. An amine compatible silicone adhesive is preferred for use with drugs, such as nicotine, which contain amine groups. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). See also Pfister, W.R., et al. "Silicon Adhesives for Transdermal Drug Delivery" Chemistry in Britain (Jan. 1991), pp. 43-46 and EP Pub. No. 0524776 A1. Suitable commercially available silicone pressure sensitive adhesives are available from Dew Corning under the trademark BIO-PSA. The silicone pressure sensitive adhesives are supplied commercially as solutions in a solvent. Per the present invention the solvent should be hexane. The thickness of layer 12 will usually be in the range of about 25 to 100 microns, more usually 50 to 75 microns. Expressed alternatively, the layer 12 will be present at about 4 to 18 mg/cm², more usually 8 to 14 mg/cm². Adhesive layer 12 initially (before it is laminated to adhesive layer 13) contains the entire drug loading. In this regard, the drug(s) will usually be added to the silicone adhesive in amounts ranging between about 5% to 50% by weight, more usually 10% to 30% by weight, based on the total dry weight of drug and adhesive.

Adhesive layer 13 is made from one or more solution acrylic pressure sensitive adhesives. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 396-456 (D. Satas, ed.) Van Nostrand Reinhold, New

York (1989). They are usually copolymers composed of: 50% to 90% of a main acrylate or methacrylate monomer, usually 2-ethylhexyl acrylate, butylacrylate, or iso-octyl acrylate: 10% to 40% of a modifying monomer such as vinyl acetate; and 2% to 20% of a functional group-containing monomer such as acrylic acid. Examples of suitable commercially available solution acrylic pressure sensitive adhesives are: National Starch DuroTak® adhesives 87-2194 and 87-2070. The thickness of the acrylic adhesive layer 13 will usually be about the same as that of layer 12. After lamination to the silicone adhesive layer 12 and equilibration of the drug between layers 12 and 13, layer 13 will also contain drug. In this regard the drug will usually constitute about 2.5% to 30% by weight, preferably 5% to 15% by weight, of layer 13 after equilibration occurs.

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The release liner layer 14 is removed before device 10 is placed on the skin. After layer 14 is removed the lower surface of layer 13 is exposed and defines the basal surface of the device which is intended to be placed directly in contact with the skin. Release liner layers are well known in the transdermal patch art. They are made of materials that permit the layer to be easily stripped or peeled away from the adjacent pressure sensitive adhesive layer. Release liner layers are typically made from drug impermeable polymers such as polyesters which are coated with materials such as silicone or fluorinated hydrocarbons that reduce the adhesiveness between it and the adjacent pressure sensitive adhesive layer. In this regard since the acrylic pressure sensitive adhesive layer rather than the silicone pressure sensitive adhesive layer defines the basal surface of the device it is possible to use a siliconized release liner. Such liners are generally not compatible with silicone adhesives. Siliconized liners are more economical than fluorocarbon coated liners. Further, use of the acrylic pressure sensitive adhesive as the basal layer provides a more controlled and predetermined delivery of the drug than could be achieved using a silicone adhesive basal layer. The particular drug release profile from the patch can be varied by altering the thickness and/or composition of the acrylic pressure sensitive adhesive layer and/or the drug loading, and/or by employing a permeation enhancer.

The drug is released from the surface of the acrylic pressure sensitive adhesive to the skin at a therapeutically effective rate. That rate will depend upon the particular drug. In the case of nicotine, the rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr. In the case of co-administration of nicotine and the mecamylamine, the nicotine rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr, and the mecamylamine rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of

mecamylamine alone, the rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of selegiline, the rate will usually be in the range of 0.2 to 3 mg/day. The flux (rate per unit area) of drug from the basal surface of the acrylic pressure sensitive adhesive and the area of that surface are matched to provide the desired rate of drug administration. As indicated, the flux may be varied by altering the drug loading, composition and/or thickness of the acrylic pressure sensitive adhesive layer, and/or by the use of permeation enhancers. The surface area of the layer in diffusional contact with the skin will usually be in the range of 5 to 100 cm², more usually in the range of about 10 to 50 cm². Each patch may be applied to the skin for periods of from several hours up to about a week, and more preferably for about 1 to 3 days.

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The patches of the invention are made in the following manner. The drug(s) is dissolved in the desired proportion(s) in a hexane solution of the pressure sensitive silicone adhesive. The drug(s) will normally constitute about 2.5% to 25% by weight of the solution. This solution is then cast onto the backing layer and allowed to dry. By casting the drug and silicone adhesive from a hexane solution, very low casting and drying temperatures (30°C to 40°C) may be used, thus reducing degradation or loss of the liquid drug(s) during the casting and drying process. Even though low processing temperatures in the 30°C to 40°C range are used. low residual hexane levels (e.g., < 0.1 % by wt.) are found in the layer after about 1 to 5 min. of drying. Other solvents, such as heptane and toluene, are not suitable since they require higher processing temperatures and thus result in more drug degradation and/or evaporation during coating and drying. Other pressure sensitive adhesives such as acrylics or polyisobutylenes are similarly not suitable for formulating liquid drugs since they require higher processing temperatures to remove their solvents (e.g., ethyl acetate, heptane, etc.). The silicone adhesive also has excellent adhesion to the backing. A solution of the acrylic pressure sensitive adhesive is cast onto a siliconized release liner layer and permitted to dry. The acrylic pressure sensitive adhesive/release liner subassembly is then laminated to the drug-containing silicone pressure sensitive adhesive/backing subassembly to form the final laminated composite. After lamination the drug(s) equilibrates in the adjacent adhesive layers. Patches are cut/punched from the composite and placed in appropriate packaging.

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Alternatively, the drug and silicone adhesive solution can be cast onto a disposable liner and dried as described. The sub-assembly can be laminated to the acrylic pressure sensitive adhesive/release liner subassembly. The disposable liner is then removed to expose the top surface of the silicone adhesive layer. A backing is then laminated to the top surface of the

silicone adhesive layer to form the final laminated composite. In still another alternative manufacturing scheme, the solution of silicone adhesive and drug is cast directly into the acrylic pressure sensitive adhesive release liner subassembly and dried. A backing is then applied to form the completed laminated composite.

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It has surprisingly been found that, in the treatment of nicotine dependence, women respond more favorably to a patch that combines nicotine and mecamylamine than to a patch that contains either nicotine or mecamylamine alone. The patch can be administered while the woman continues to smoke and then ceases smoking or if she chooses to stop smoking at the same time as beginning treatment.

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For treatment of nicotine dependence, the patches of the invention are typically worn for a total period of about 3 to 16 weeks. During the first 1 to 4 weeks, preferably 2 to 3 weeks, the patent is allowed to smoke as desired. During the remainder of the treatment, i.e., two to 12 weeks, preferably 4 to 8 weeks, the patient is advised to not smoke.

EXAMPLES

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The following examples further illustrate the patches of the invention and the process used to make them. These examples are not intended to limit the invention in any manner.

Example 1: Preparation and Testing of Nicotine Patch

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Nicotine was added to a hexane solution of Dow Corning BIO-PSA amine-compatible silicone pressure sensitive adhesive to a level of approximately 12% by weight based on the combined dry weight of adhesive and nicotine. The resulting hexane solution of adhesive and nicotine was coated onto a 3M Scotchpak 1109 polyester/polyolefin backing at 13.8 mg/cm² (1.63 mg/cm² nicotine and 12.17 mg/cm² adhesive) and the coated backing was dried at 30°C to 40°C for about 3 min.

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National Starch DuroTak 87 2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coater Products 1-5 PESTR (Matte) - 164Z siliconized polyester release liner at 13.18 mg/cm² and the coated release liner was dried at 100°C for about 10 min.

The dried silicone adhesive/nicotine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the nicotine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of nicotine within the layers was about 6% (w/w) after equilibration.

In vitro nicotine flux from the laminated composite was determined at 32°C through human cadaver epidermis into an infinite sink using modified Franz glass diffusion cells. Nicotine assays were made by HPLC.

For comparison purposes the flux of nicotine from commercial Habitrol3 21 mg/day patches was determined using the same test procedure. Figure 2 is a graph of the nicotine flux from the composite of the example and from the Habitrol3 patches versus time.

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Example 2: Preparation and Testing of Nicotine/Mecamylamine Patches
Nicotine and mecamylamine were added to a hexane solution of Dow Corning BIO-PSA
amine compatible silicone pressure sensitive adhesive. Two batches were made: one contained
approximately 10% nicotine and 6.4% mecamylamine based on the total dry weight of the
adhesive and the two drugs: and a second contained approximately 10% nicotine and 4.2%
mecamylamine, based on the total dry weight of the adhesive and the two drugs. The batches
were separately coated onto a 3M Scotchpak 1109 polyester/polyoefin backing film at 9.6
mg/cm² (0.96 mg/cm² nicotine, 0.61 mg/cm² mecamylamine, 8.03 mg/cm² adhesive for the first
batch; 0.96 mg/cm² nicotine, 0.40 mg/cm² mecamylamine, 8.24 mg/cm² adhesive for the second
batch) and then dried at 30 to 40°C for about 2 min.

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A blend of two National Starch DuroTak acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated at 8.0 mg/cm² onto a 75 micron thick Daubert Coater Products siliconized polyester release liner (1-3 PESTR (Matte) - 164Z) and dried at about 100°C for about 10 min.

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The drug-containing silicone adhesive/backing subassembly was then laminated to the acrylic adhesive/release liner subassembly to form a four layer/laminated composite. After lamination the nicotine and mecamylamine distributed themselves uniformly within the adjacent

adhesive layers. The concentration of the drugs in the adhesive layers after equilibration was: nicotine. 5.45% (w/w) and mecamylamine 3.47% (w/w) for the composite made from the first batch and 5.45% (w/w) and 2.27% (w/w), respectively, for the composite made from the second batch. Patches about 23 cm² in area were cut from the composites. These patches were designed to deliver 21 mg of nicotine and 6 mg of mecamylamine in 24 hr and 21 mg of nicotine and 3 mg of mecamylamine in 24 hr, respectively.

Nicotine and mecamylamine fluxes from the patches were determined using the procedure described Example 1. Mecamylamine assays were made by GC. Figure 3 is a graph showing the nicotine flux from the patches versus time. Patches made from the first batch composite are designated 21/6; those from the second batch composite are designated 21/3. Figure 4 similarly is a graph showing the mecamylamine flux from the patches.

Example 3 Preparation and Testing of Selegiline Patch

Selegiline was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 10% by weight based on the combined dry weight of adhesive and selegiline. The resulting hexane solution of adhesive and selegiline was coated on 3M Scotchpak 1109 polyester/polyolefin backing at 10.0 mg/cm² (1.0 mg/cm² selegiline and 9.0 mg/cm² adhesive) and the coated backing was dried at 30°C to 40°C for about 3 minutes.

National Starch DuroTak® 87-2194 acrylic solution pressure sensitive adfresive was coated onto a 125 micron thick Daubert Coated Products 1-5 PESTER (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm² and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/selegiline-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the selegiline distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of selegiline within the layers in about 5.5% (w/w) after equilibration.

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Selegiline flux from the patches was determined using the procedure described in Example 1. Selegiline assays were made by HPLC.

Figure 5 is a graph of the selegiline flux from the composite of this example versus time.

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Example 4. Preparation and Testing of Mecamylamine Patch

Mecamylamine was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 6.3% by weight based on the combined dry weight of adhesive and mecamylamine. The resulting hexane solution of adhesive and mecamylamine was coated on 3M Scotchpack 1109 polyester/polyolefin backing at 9.6 mg/cm² (0.61 mg/cm² mecamylamine and 8.99 mg/cm² adhesive) and the coating backed was dried at 30°C to 40°C for about 3 minutes.

A blend of two National Starch DuroTak® acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w. respectively, was made. The blend was coated onto a 75 micron thick Daubert Coated Products 1-2 PESTR (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm² and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/mecamylamine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the mecamylamine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of mecamylamine within the layers is about 3.47% (w/w) after equilibration. Patches about 23 cm² in area were cut from the composites. These patches were designed to deliver 6 mg of mecamylamine in 24 hr.

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Mecamylamine flux from the patches was determined using the procedure described in Example 1. The mecamylamine assay was done by gas chromotography. Figure 6 is a graph of the mecamylamine flux from the composite of this example versus time; mecamylamine flux through the same section of cadaver skin from the 21/3 and 21/6 compositions of Example 2 are shown for comparison.

Study A.

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Patches made according to Examples 1, 2 and 4 and a placebo patch were subject to a clinical study. The study was a multi-center, double-blind, randomized parallel group study. Patients were randomized to receive one of five treatments: nicotine/mecamylamine 21/6: nicotine/mecamylamine 21/3; nicotine (21 mg/24 hr); mecamylamine (6 mg/24 hr) and placebo. Patches were applied daily for the first six weeks of the study. Patients were instructed to continue smoking for the first two weeks and to stop smoking thereafter.

Among the efficacy parameters monitored during the study were four week continuous abstinence after the quit smoking date, nicotine plasma concentration, and ad hoc smoking during the treatment period.

Table 1 below provides the overall abstinence data for the study. In the table "N" represents the number of patients, "No" indicates non-abstinence and "Yes" indicates abstinence. As indicated the nicotine/mecamylamine 21/6 gave the highest abstinence.

Table 1

	Overall	21/6	21/3	21/0	0/6	Pla
N	705	142	141	141	140	141
No	82%	74%	79%	79%	82%	92%
Yes	18%	26%	21%	21%	18%	8%

Figure 7 is a graph showing the mean nicotine plasma concentrations in ng/ml of the patients by treatment and time. As shown, the mecamylamine only patch (0/6) produced a steady decline in nicotine levels even during the initial two-week period of the study. Fig. 8 is a graph showing the mean observed change in the number of cigarettes smoked by treatment and day. Surprisingly, the number of cigarettes smoked did not increase with the mecamylamine only (0/6) treatment, as the literature reports that oral mecamylamine administration increased ad hoc cigarette consumption.

Study B.

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A second multi-center, double-blind, randomized parallel group clinical study was conducted. Patients were randomized to receive one of three treatments: nicotine/mecamylamine 21/6; nicotine/mecamylamine 21/3, and nicotine (21 mg/24 hr). Patient instructions were the same as in the first study.

The abstinence data for this study are summarized in Table 2. In this study the nicotine/mecamylamine combination was again more effective than nicotine alone.

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Table 2

Treatment		21/6	21/3	21/0
11000000	1	21/0	21/3	21/0
				1
N		180	180	180
Abstinence	2	29%	29%	23%
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A detailed examination of the data the clinical studies yielded a surprising difference in abstinence rates for females and males. In both studies, the abstinence rate for females in the 21/6 treatment group was 31% compared to the 21/0 treatment group rates of 17% in the first study and 18% in the second study. These gender specific data are summarized in Table 3.

Table 3

Study	Gender		21/6	21/3	21/0	0.6	Plac
						1	
First	Female	N	70	67	63	75	74
		% Abst.	31	16	17	17	9
	Male	N	72	74	78	65	67
		% Abst.	21	26	24	18	6
Second	Female	N	93	96	91		
		% Abst.	31	29	18		
	Male	N	87	84	89		
	-1-	% Abst.	28	29	28	 	

N = number of subjects in study.

5 % Abst.= Four-week continuous abstinence results.

Modifications of the above described modes for carrying out the invention that are obvious to persons of skill in the transdermal patch art are intended to be within the scope of the following claims. All publications, patent applications and patents noted above are hereby incorporated by reference.

<u>CLAIMS</u>

- 1. A transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:
 - a) a top backing layer that is impermeable to the drug;
- b) an intermediate silicone adhesive layer containing the drug and underlying the backing layer:
- c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and
- d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.
- 2. The transdermal patch of claim 1, wherein the drug is nicotine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour to the patient.
- 3. The transdermal patch of claim 1, wherein the drug is a combination of nicotine and mecamylamine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour and 0.02 to 1 mg mecamylamine per hour to the patient.
- 4. The transdermal patch of claim 1 wherein the drug is selegiline and the patch is capable of administering 0.2 to 3 mg selegiline per day to the patient.
- 5. The patch of claim 1 wherein the drug is mecamylamine only and the patch is capable of administering 0.02 to 1 mg mecamylamine per hour to the patient.
 - 6. The patch of claim 1 wherein the release liner layer is a siliconized release liner layer.
- 7. The patch of claim 1 wherein the acrylic adhesive layer is made from a blend of two acrylic adhesives.

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8. A method of making a transdermal patch for administering a volatile liquid drug to a patient comprising:

- a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;
- b) evaporating the hexane from the coating to form a layer of drug-containing silicone adhesive on the backing layer; and
- c) laminating an assembly comprising an acrylic adhesive coated onto a release liner layer onto the silicone adhesive layer on the backing layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.
 - 9. The method of claim 8 wherein step b) is carried out at 30°C to 40°C.
- 10. The method of claim 8 wherein the release liner layer is a siliconized release liner layer.
 - 11. The method of claim 8 wherein the drug is nicotine.

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- 12. The method of claim 8 wherein the drug is a combination of nicotine and mecamylamine.
 - 13. The method of claim 8 wherein the drug is selegiline.
 - 14. The method of claim 8 wherein the drug is mecamylamine only.

- 25 15. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal coadministration of nicotine to the person.
- 16. The method of claim 15 wherein the rate of mecamylamine administration is 0.02 to1 mg/hr.
 - 17. The method of claim 15 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr.

18. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine to the person for a first time period during which the person smokes cigarettes as desired and continuing said administration for a second time period during which the person is advised to not smoke.

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- 19. The method of claim 18 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.
- 20. The method of claim 18 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.
 - 21. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman.

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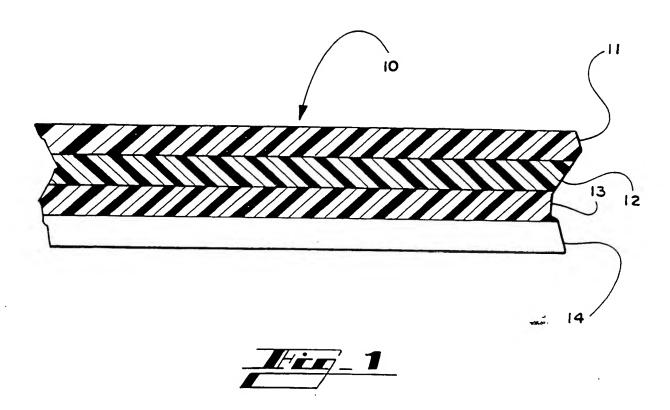
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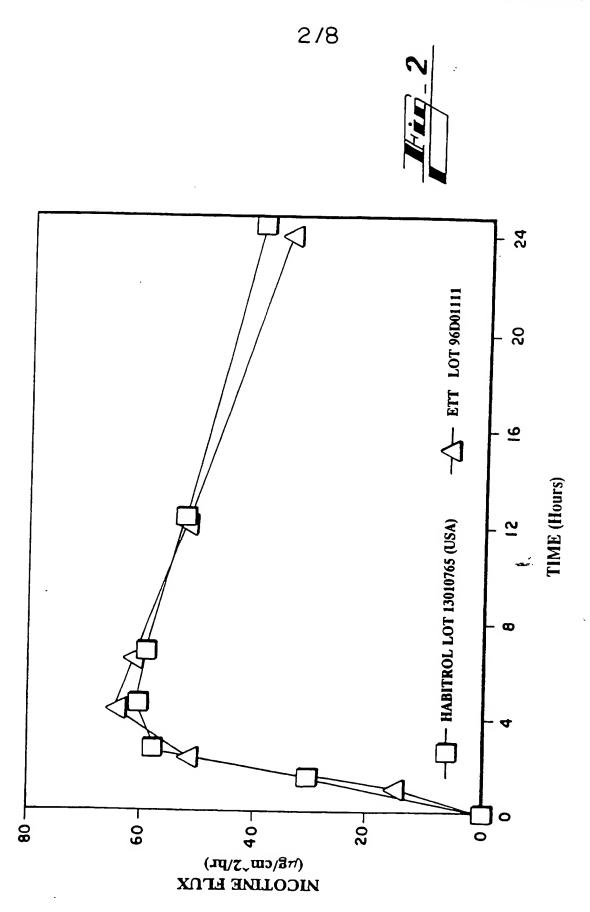
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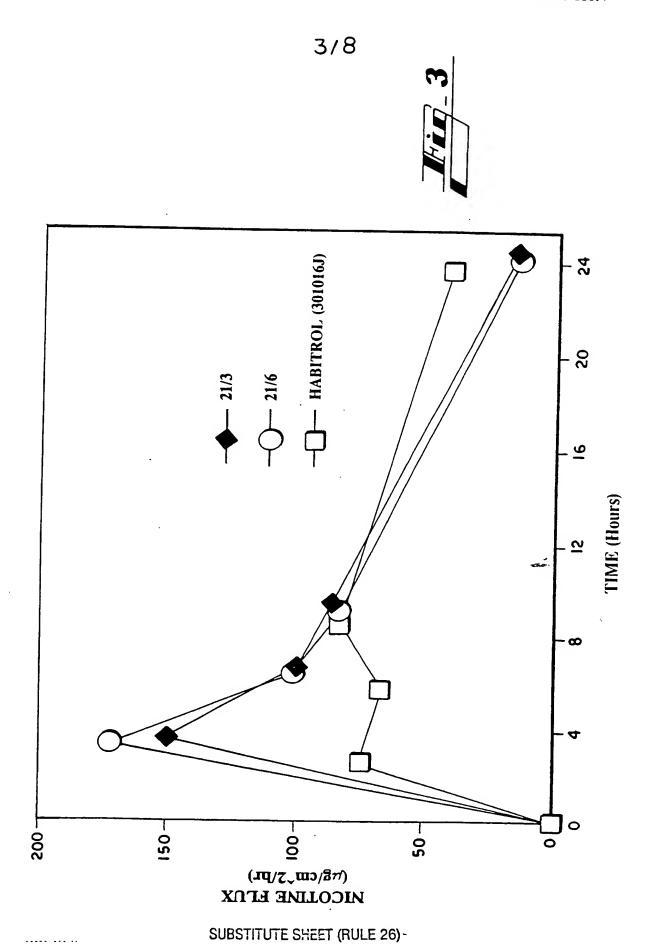
- 22. The method of claim 21 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr and the rate of nicotine administration is 0.2 to 1.5 mg/hr.
- 23. The method of claim 21 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr and the rate of nicotine administration is 0.3 to 0.9 mg/hr.
 - 24. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman for a first time period during which the woman smokes cigarettes as desired and continuing said administration for a second time period during which the woman is advised to not smoke.
 - 25. The method of claim 24 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.

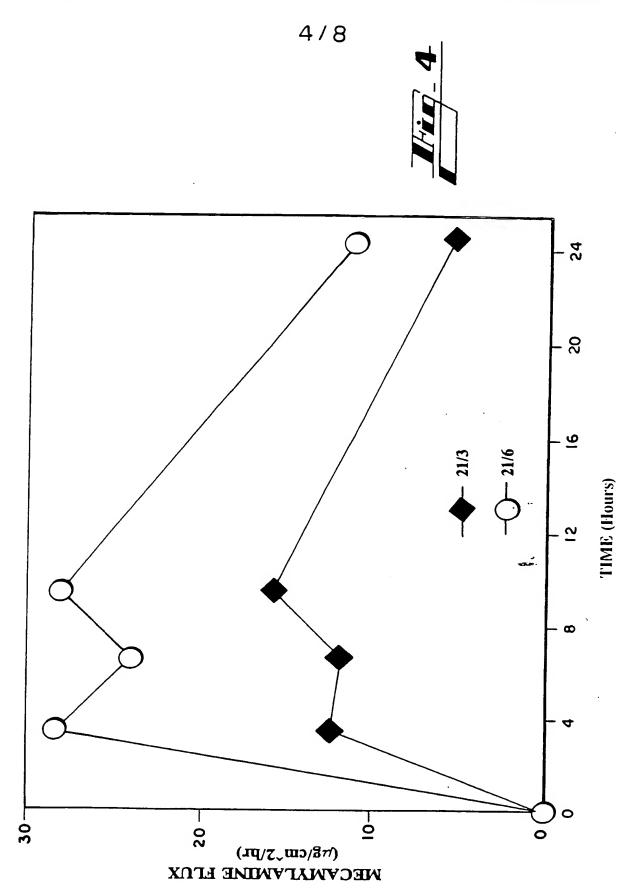
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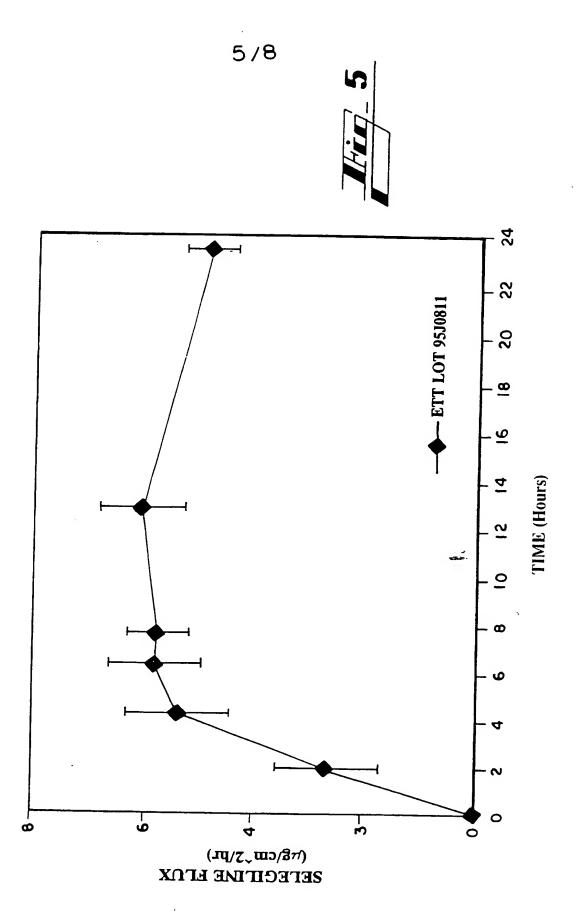
26. The method of claim 24 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.

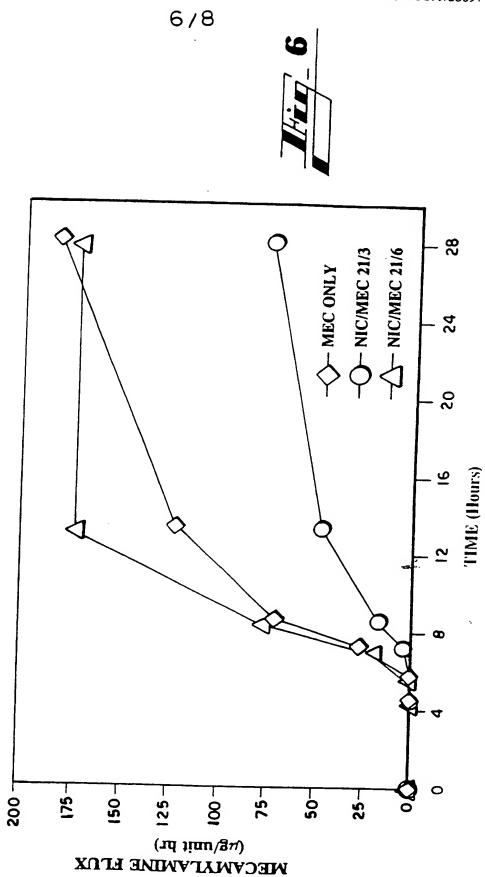


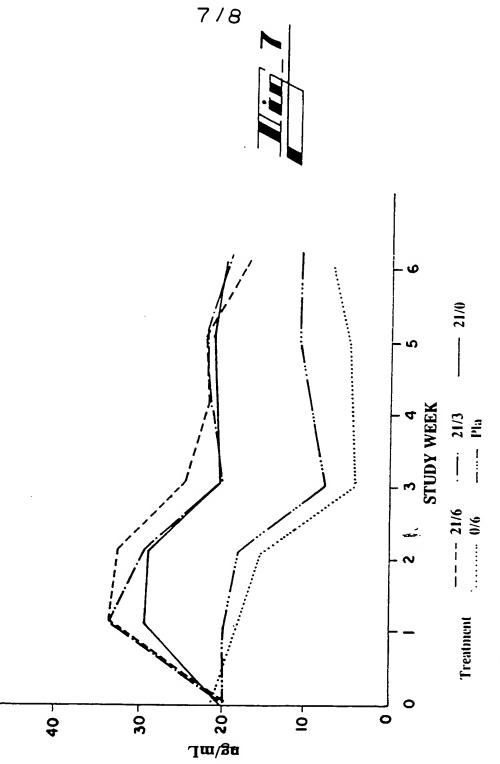




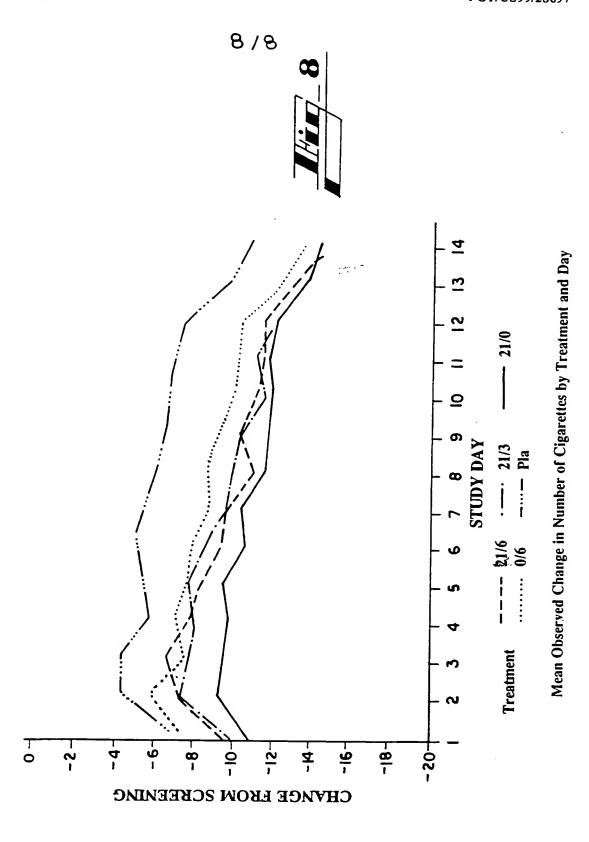








Mean Nicotine Plasma Concentration by Treatment and Study Week



INTERNATIONAL SEARCH REPORT

Inc. Jacob Application No PCT/US 99/28697

			PCT/US 99/28697
A. CI.A	ASSIFICATION OF SUBJECT MATTER		
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C. DOCU	MENTS CONSIDERED TO BE RELEVANT		
Caregory .	Citation of document, with indication, where appropriate, of the	c relevant passages	· Relevant to claim No.
x	WO 96/40085 A (NOVEN PHARMACEUTICAL 19 December 1996, page 8, line 14 - pag page 18, line 32 - pa line 2, page 19, line examples 2-4, claims	ge 9, ge 19, s 18-37,	1,2, 4,6-8, 10,11, 13
Y	9,10,17,19-21,24.		3,5
x	WO 93/00058 A (NOVEN PHARMACEUTICAL 07 January 1993, page 24, line 9, clai 14-19,37-39,53-64,91-	ms 1-5,	1,2, 4,6
Y	14-19,37-39,33-64,91-	93.	3,5
Y	US 4717568 A (ECKENHOFF ET AL.)		3,5
X Furu	her documents are listed in the continuation of box C.	Patent famuly me	mbers are listed in annex.
"A" docume consider of filing of the citation	ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another in or other special reason (as specified) controlled to the publication of controlled to the publication of the special reason (as specified) controlled to the publication of the special reason (as specified) controlled to the publication of the special reason (as spec	or priority date and recited to understand the invention. 'X' document of particular cannot be considered involve an inventive. 'Y' document of particular cannot be considered document is combined ments, such combination the art. '&' document member of	international search report
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INTERNATIONAL SEARCH REPORT

Intern nal Application No

PCT/US 99/28697

C.(Conunua	uon) DOCUMENTS CONSIDERED TO BE RELEVANT	PCT/US 99/2869/
Caregory .	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
x	05 January 1988, abstract, column 18, lines 25,26. US 5691365 A (CROOKS ET AL.) 25 November 1997, abstract, column 4, lines 20-29, column 14, lines 50-67, column 16, line 63.	15-20
x	US 5316759 A (ROSE ET AL.) 31 May 1994, abstract, claims.	21-26
A	US 5230898 A (HORSTMANN ET AL.) 27 July 1993, the whole document.	1-26
A	US 5176915 A (HOFFMANN) 05 January 1993, the whole document.	1-26

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Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La presente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l' Office.

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WO A2 9640085 19-12-1996 AU A1 60289/96 30-12-1996 WO A3 9640085 13-03-1997 CA AA 2223588 19-12-1996 EP A2 833671 08-04-1998 15-06-1998 II A0 122484 15-06-1999 WO A1 9300058 07-01-1993 AU A1 22689/92 25-01-1993 AU A1 22689/92 25-01-1996 BR A 206208 22-11-1994 AU A1 22689/92 25-01-1996 BR A 206208 22-11-1994 AU A1 591432 13-04-1994 A 19-1994 A EP A1 591432 17-05-1995 FI A 935833 23-12-1993 FI A 935833 23-12-1993 A A 410-1993 A MX A1 9203648 31-00-1994 A 17-11-1994 A A 1	Patent document cited in search report Document de brevet cité	Veröffentlichung Publication date Date de		Pat Pat mi Mem	entfamilie ent family ember(s) bre(s) de la	Veröffentlichung Publication date Date de
WO A3 9640085 13-03-1997		19-12-1996	AU	A1	60289/96	<u> </u>
FP A2 833671 08-04-1998 15-06-1998 15-06-1998 15-06-1999	WO A3 9640085					
IL						
WO Al 9300058 07-01-1993 AU Al 22689/92 25-01-1993 AU B2 670033 04-07-1996 BR A 9206208 22-11-1994 CA AL 2110914 07-01-1993 EP AL 591432 13-04-1994 EP AL 591432 17-05-1995 EP AL 591432 17-01-1995 EP AL 591432 EP SI 418248 EP -07-7-1994 EP AL 591432 EP AL 591432 EP AL 591432 EP BL 591432 EP BL 591432 EP BL 591432 EP SI 418248 EP -02-1999 EP AL 591432 EP BL 591432 EP SI 418248 EP -02-1999 EP AL 591432						
## A1 9300058 07-01-1993 AU						
AU B2 670033 04-07-1996 BR A 9206208 22-11-1994 CA AA 2110914 07-01-1993 EP A1 591432 13-04-1995 EP A1 591432 13-04-1995 FI A 935833 23-12-1993 FI A0 935833 23-12-1993 IL A0 102277 14-01-1993 JP T2 6510279 17-11-1994 MX A1 9203648 31-01-1995 NO A0 934523 10-02-1993 NO A 934523 10-12-1993 NO A 934523 10-12-1993 SG A1 49164 18-05-1998 US A 5474783 12-12-1998 US A 5958446 28-09-1999 US A 5656286 12-08-1999 US A 6024976 15-01-1994 AT E 99176 15-01-1994 AT E 99176 15-01-1994 AU A1 32847/89 22-09-1989 AU B2 606840 14-02-1991 DE T2 68911920 07-07-1994 DE T2 68911920 07-07-1999 DE T2 68911920 07-07-07-1999 DE T2 68911920 07-07-07-1999 DE T2 68911920 07-07-07-1999 DE T2 68911920 07-07-07-1999 D	WO A1 9300058	07-01-1993				
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US A 4814168 21-03-1989 WO A1 8907950 08-09-1989 US A 4994278 19-02-1991 US A 4994267 19-02-1991 US A 5032207 16-07-1991 US A 5300291 05-04-1994 US A 5405486 11-04-1995 US A 5656285 12-08-1997						
WO A1 8907950 08-09-1989 US A 4994278 19-02-1991 US A 4994267 19-02-1991 US A 5032207 16-07-1991 US A 5300291 05-04-1994 US A 5405486 11-04-1995 US A 5656285 12-08-1997						08-11-1995
US A 4994278 19-02-1991 US A 4994267 19-02-1991 US A 5032207 16-07-1991 US A 5300291 05-04-1994 US A 5405486 11-04-1995 US A 5656285 12-08-1997						
US A 4994267 19-02-1991 US A 5032207 16-07-1991 US A 5300291 05-04-1994 US A 5405486 11-04-1995 US A 5656285 12-08-1997						
US A 5032207 16-07-1991 US A 5300291 05-04-1994 US A 5405486 11-04-1995 US A 5656285 12-08-1997						
US A 5300291 05-04-1994 US A 5405486 11-04-1995 US A 5656285 12-08-1997						
US A 5405486 11-04-1995 US A 5656285 12-08-1997						
US A 5656285 12-08-1997						
12-00-1997						
03 A 3000039 11-11-1997						
			- 03		2000033	11-11-1997

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentlamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

This annex fists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La presente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l'Office.

				de l' Office.		
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	peführte Patentdokumente Patent document cited in search report Document de brevet cité Veröffentlichung Publication date Date de			lied(er) der entfamilie ent family ember(s) bre(s) de la e de brevets	Datum der Veröffentlichung Publication date Date de publication	
		US	Α	5719197	17-02-1998	
		AT	E	122240	15-05-1995	
		AU	A1	50349/90	13-08-1990	
		AU	B2	632534	07-01-1993	
		CA	AA	2044132	12-07-1990	
		CA	С	2044132	06-05-1997	
		DE	C0	69019175	14-06-1995	
		DE	Т2	69019175	18-01-1996	
		DK	Т3	379045	09-10-1995	
		EP	A1	379045	25-07-1990	
		EP	Al	453505	30-10-1991	
		EP	A1	634179	18-01-1995	
		EP	B1	379045	10-05-1995	
		ES	Т3	2071683	01-07-1995	
ŧ		HK	A1	1006155	12-02-1999	
		IE JP	B	69048	07-08-1996	
		JP JP	T2	4502719	21-05-1992	
		NL	B4	7093939	11-10-1995	
		PT	A A	9020159	02-01-1991	
		PT	В	92830 92830	31-07-1990	
		WO	A1	9007940	29-12-1995	
		AU	A1	54206/90	26-07-1990	
		BR	A	9008012	21-10-1991	
		DK	Т3	474647	01-12-1992	
		EP	Bl	474647	18-08-1997	
		FI	A	924313	05-02-1997	
		FI	A0	924313	25-09-1992 25-09-1992	
		WO	A1	9114463	03-10-1991	
		DE	CO	69029909	20-03-1997	
		DE	T2	69029909	11-09-1997	
		EP	Al	474647	18-03-1992	
		NO	A0	923699	24-09-1992	
		NO	A	923699	01-02-1993	
		ΑU	A1	15212/95	01-08-1995	
		υA	B2	700429	07-01-1999	
		BR	Α	9506470	07-10-1997	
		CA	AA	2180530	13-07-1995	
		CN	A	1143318	19-02-1997	
		EP	Al	737066	16-10-1996	
		FI	A0	962770	05-07-1996	
		FI	A	962770	29-08-1996	
		HU HU	A0	9601856	30-09-1996	
		IL	A2	74913	28-03-1997	
		JP	AO TO	112269	30-03-1995	
		NO	T2 A0	9511987 962833	02-12-1997	
		00	AU A	962833	05-07-1996	
		NZ	A	278769	15-08-1996	
				210103	27-04-1998	

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

ANNEX

To the International Search Report to the international Patent Application No.

PCT/US 99/28697 SAE 268121

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ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

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Im Postoret t t		de l'Office.					
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report	Datum der Veröffentlichung Publication date		Pate Pate	ed(er) der entfamilie ent family mber(s)	Datum der Veröffentlichung Publication		
Document de brevet cité	Date de	1		re(s) de la	date		
dans le rapport de recherche	publication			de brevets	Date de publication		
		SG	A1	49331	18-05-1998		
		WO	A.1	9518603	13-07-1995		
		ZA	A.	9500108	25-03-1996		
		CA	AA	2025033	16-03-1991		
		AU	A1	20040/92	21-12-1992		
		CA	AA	2109099	26-10-1992		
		EP	A1	592481			
		SG	A1	43349	20-04-1994		
		WO	A1	9219451	17-10-1997		
		CA	AA	2126366	12-11-1992		
		AT	E	144704	22-12-1994		
		AU	A1		15-11-1996		
		AU	52	14610/92 658870	06-10-1992		
		UA UA	A1	28331/95	04-05-1995		
		AU	B2		28-09-1995		
		CA	AA	694243	16-07-1998		
		DE	C0	2104474	28-08-1992		
				69214938	05-12-1996		
		DE	T2	69214938	15-05-1997		
		DK	T3	573576	01-04-1997		
		EP EP	A1	573576	15-12-1993		
			A2	728477	28-08-1996		
		EP EP	A3	728477	11-09-1996		
			E1	573576	30-10-1996		
		ES	T3	2094906	01-02-1997		
		FI FI	A.	933761	26 <u>-08</u> -1993		
		GR	A0	933761	26-08-1993		
			TΞ	3022708	31-05-1997		
		JP	T2	6508820	06-10-1994		
		МО	0.A	933296	16-09-1993		
		МО	A	933296	01-11-1993		
		ИО	B1	307363	27-03-2000		
		SG	Al	49158	18-05-1998		
		WO	Al.	9215289	17-09-1992		
		US	A.	5234957	10-08-1993		
		US	A	5332576	26-07-1994		
		US	A.	5446070	29-08-1995		
		AU	A1	76722/94	21-03-1995		
		CA	AA.	2170504	02-03-1995		
		WO	Al	9505813	02-03-1995		
		WO	A.1	9640084	19-12 - 1996		
		WO	Al	9606602	07-03-1996		
		AU	A.1	60290/96	30-12-1996		
		WO	A2	9640086	19-12-1996		
		WO	εA	9640086	13-02-1997		
		ZA	A	9604735	19-12-1996		
		AT	E	148633	15-02-1997		
		ES	тЗ	2097145	01-04-1997		
		ΑU	Al	34168/95	22-03-1996		
		CA	Αř.	2170505	27-02-1996		

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr. ANNEX
To the International Search
Report to the international Patent
Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

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La presente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l' Office.

I D	T	т		de l' Office.		
Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	tumente Veröffentlichung publication date			lied(er) der tentfamilie tent family ember(s) bre(s) de la e de brevets	Datum der Veröffentlichung Publication date Date de publication	
US A 4717568	05-01-1988	AU	A1			
	70 01 1500	AU AU	B2	39242/85	26-09-1985	
		BE	. A1	571400	14-04-1988	
		CA	Al	901941 1221587	01-07-1985	
		DE	Al	3509410	12-05-1987	
		DE	C2	3509410	26-09-1985	
		ES	Al	540185	20-03-1997	
		ES	A5	540185	16-11-1985	
		ES	A1	8602388	16-12-1985	
		FR	Al	2561103	16-03-1986	
		FR	B1	2561103	20-09-1985	
		GB	A0	8431661	07-04-1989	
		GB	Al	2155787	30-01-1985	
		GB	B2	2155787	02-10-1985	
		IT	A0	8567263	16-12-1987	
		IT	A	1185795	18-03-1985	
		JP	A2	60236665	18-11-1987	
		J₽	B4	6041406	25-11-1985	
		MX	A.	161579	01-06-1994	
		NL	A	8500697	12-11-1990	
		NZ	A	210601	16-10-1985	
		US	A	4595583	08-01-1988	
		ZA	A	8409802	17-06-1986	
		US	A	4612186	28-08-1985	
		US	A	4624945	16-09-1986	
		US	A	4684524	25-11-1986	
		US	A	4692336	04-08-1987	
		US	A	4717566	08-09-1987	
		US	A	4717718	05-01-1988	
		US	A	4729793	05-01-1988	
		US	A	4772474	08-03-1988	
		US	A	4844984	20-09-1988 04-07-1989	
		US	Α	4927633		
		US	Α	5000957	22-05-1990 19-03-1991	
		AR	A1	240399	30-04-1990	
		ΑU	A1	60697/86	12-02-1987	
		AU	B2	591511	07-12-1989	
		BE	Al	905249		
		BR	A	8603678	01-12-1986	
		CA	Al	1278968	10-03-1987 15-01-1991	
		DE	A1	3625915		
		DE	C2	3625915	19-02-1987	
		ES	Al	556303	24-04-1997	
		ES	A5	556303	16-10-1987	
		ES	Al	8800042	16-11-1987	
		FR	Al	2585950	01-01-1988	
		FR	B1	2585950	13-02-1987	
		L 11				
		GB	A0	8618350	03-03-1989 03-09-1986	

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr. This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report.
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La presente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l' Office.

			de i Office.					
angeführte Patentdokumente Verö Patent document cited P in search report		Datum der Veröffentlichung Publication date Date de		Pater Pater men	ed(er) der ntfamilie nt family nber(s) re(s) de la	Datum der Veröffentlichung Publication date Date de		
	port de recherche	publication			de brevets	publication		
· · · · · ·	<u> </u>	<u> </u>			2178659	<u> </u>		
			GB	B2	8667641	13-09-1989		
			IT	A0		07-08-1986		
			IT	A	1195818	27-10-1988		
			JP	A2	62039518	20-02-1987		
			JP	B4	8018972	28-02-1996		
			NL	A	8601971	02-03-1987		
			NZ	A	216991	27-09-1989		
	- 5 603 0 66		ZA	A	8605914	29-04-1987		
US A	5691365	25-11-1997			none			
US A	5316759	31-05-1994	US	A	5574052	12-11-1996		
			US	Α	5703101	30-12-1997		
			US	A	5726190	10-03-1998		
	•		US	Α	5861422	19-01-1999		
			US	Α	5935975	10-08-1999		
			US	Α	4846199	11-07-1989		
			US	A	4945928	07-08-1990		
US A	5230898	27-07-1993	AΤ	E	88911	15-05-1993		
			AU	A1	51314/90	04-10-1990		
			UA	В2	627283	20-08-1992		
			CA	AA	2013050	01-10-1990		
			CA	С	2013050	28-04-1998		
	•		CS	A2	9001483	15-10-1991		
			CZ	В6	284287	14-10-1998		
			DD	A5	293266	29-08-1991		
			DE	A1	3910543	11 -1 0-1990		
			DE	C2	3910543	07-01-1993		
			DE	C0	59001338	09-06-1993		
			DK	Т3	391172	27-09-1993		
			EP	Al	391172	10-10-1990		
			EP	Bl	391172	05-05-1993		
			ES	Т3	2055201	16-08-1994		
			FI	A0	901556	28-03-1990		
			FI	B1	103478	15-07-1999		
			HR	Al	930590	30-04-1995		
			HR	B1	930590	31-10-1997		
			HU	A0	902018	28-08-1990		
			HU	A2	54062	28-01-1991		
			HU	В	205254	28-04-1992		
			ΙE	В	65520	01-11-1995		
			IL	A0	93956	23-12-1990		
			ΙL	Al	93956	31-12-1995		
			JP	A2	3027311	05-02-1991		
			JP	B2	2552191	06-11-1996		
			KR	В1	9607517	05-06-1996		
			ИО	A0	901458	30-03-1990		
			ИО	Α	901458	02-10-1990		
			NO	В	180671	17-02-1997		
			NO	С	180671	28-05-1997		

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

ANNEX

To the International Search Report to the international Patent Application No.

PCT/US 99/28697 SAE 268121

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ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

La presente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnes à titre indicatif et n'engagent pas la responsibilité de l' Office.

Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Patentfamilie Patent family member(s) Membre(s) de la famille de brevets			Veröffentlichung Publication date Date de publication
	<u></u>	PL	B1	163297	31-03-1994
		PT	Α	93621	08-01-1991
		PT ·	В.	93621	28-06-1996
		SI	Α	9010635	30-06-1998
		US	A	5702721	30-12-1997
		YU	Α	635/90	31-10-1991
		ZA	A	9002465	30-01-1991
US A 5176915	05-01-1993	AT	E	133569	15-02-1996
05 A 5170515	•••	AU	A1	50766/90	01-11-1990
		AU	B2	622775	16-04-1992
		CA	AA	2012124	15-09-1990
		CZ	EА	9001137	17-11-1999
		DD	A5	296844	19-12-1991
		DE	Al	3908432	27-09-1990
		DE	C2	3908432	04-07-1991
		DE	C0	59010095	14-03-1996
		DK	тЗ	387694	24-06-1996
		EP	A2	387694	19-09-1990
		EP	EA	387694	28-11-1990
		EP	В1	387694	31-01-1996
		ES	Т3	2085293	01-06-1996
		FI	0A	901291	15-03-1990
		GR	Т3	3019786	31-07-1996
		HR	Al	930666	31-10-1994
		HR	В1	930666	31-08:1998
		HU	A0	901423	28-06-1990 28-12-1990
		HU	A2	53814	01-03-1993
		HU	В	206992	30-07-1997
		IE	В	74681	23-12-1990
		IL	0A	93679	23-01-1991
		JP	A2 B2	3014515 2588039	05-03-1997
		JP			08-11-1995
		KR	B1	9513462 901127	09-03-1990
		МО	A0		17-09-1990
•		NO	A	901127 232896	26-04-1991
		NZ PH	A A	26277	10-04-1992
			B1	162638	31-12-1993
		PL PT	A	93431	07-11-1990
		PT	В	93431	30-04-1996
		SI	A	9010494	30-06-1998
		2A	A	9001940	28-12-1990

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